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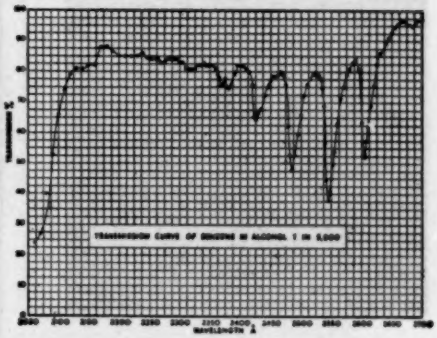

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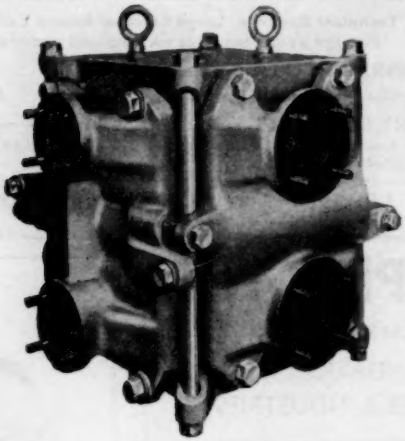

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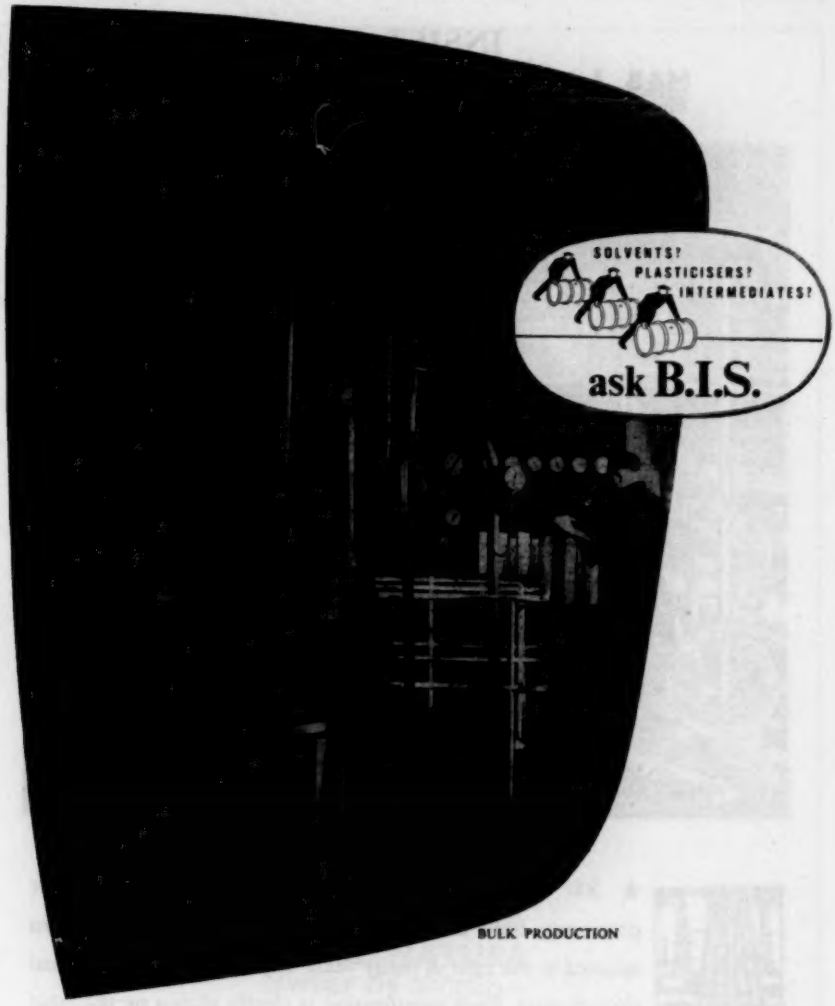

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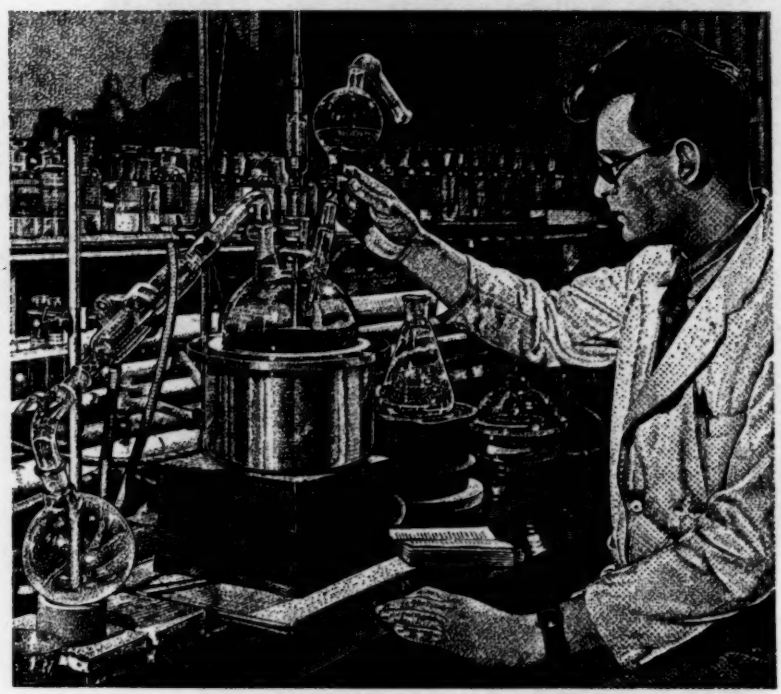

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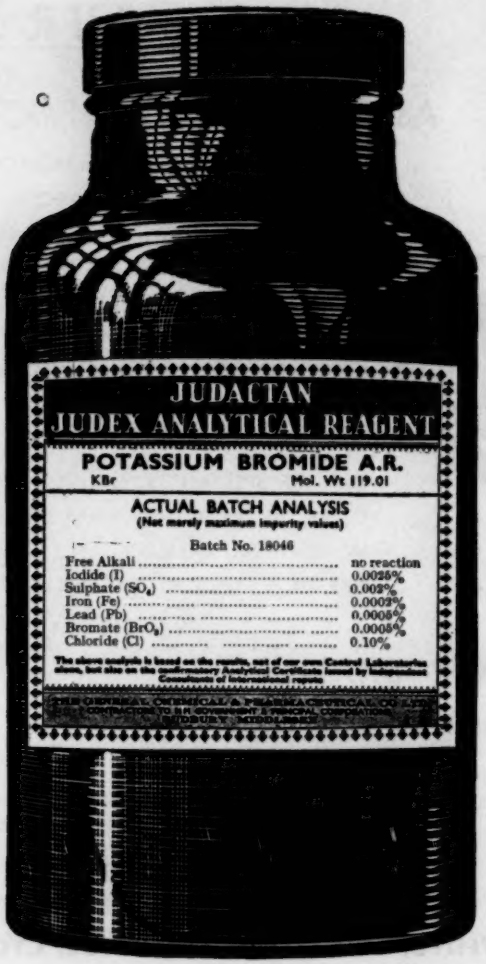

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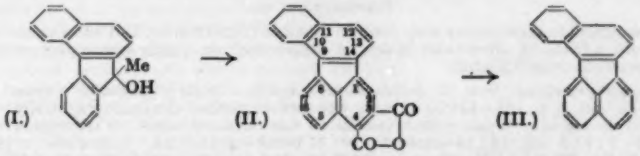
557. *A New Synthesis of* 10 : 11-*Benzofluoranthene.*

By Neil Campbell, N. M. Khanna, and A. Marks.

10 : 11-Benzofluoranthene has been synthesised from 9-methyl-3 : 4-benzofluoren-9-ol and maleic anhydride and found to be identical with products obtained in various ways by Zinke and Pack (*Monatsh.*, 1949, **80**, 213), von Braun and Kirschbaum (*Ber.*, 1921, **54**, 597), and Dansi and Ferri (*Gazzetta*, 1941, **71**, 648).

10 : 11-Benzofluoranthene (III) has been synthesised and its structure determined by Orchin and Reggel (*J. Amer. Chem. Soc.*, 1947, **69**, 505; 1951, **73**, 436). We have now prepared it by heating 9-methyl-3 : 4-benzofluoren-9-ol (I) with maleic anhydride and decarboxylating the resulting 10 : 11-benzofluoranthene-3 : 4-dicarboxylic anhydride (II) (cf. Campbell and Wang, *J.*, 1949, 1513). The identity of the hydrocarbon was established by comparison of its trinitrobenzene derivative with an authentic sample kindly supplied by Dr. Reggel. The Diels–Alder reaction results in ring closure on the benzene and not the naphthalene moiety presumably owing to the inactivity of the available β-position of the latter. The product is fully aromatic and not a dihydro-hydrocarbon as might have been expected (cf. Campbell and Wang, *loc. cit.*).



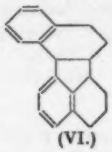
We have proved that three hydrocarbons prepared by other methods are undoubtedly 10 : 11-benzofluoranthene. Zinke and Pack (*Monatsh.*, 1949, **80**, 213) by the zinc dust distillation of a substance previously regarded as 1-hydroxyperylene obtained a yellow hydrocarbon, m. p. 165—167°, which they tentatively regarded as 10 : 11-benzofluoranthene. We have found a sample, which Professor Dr. Zinke was good enough to send us, to be identical with our compound.

Orchin and Reggel (*loc. cit.*, 1947; see also Bell and Hunter, *J.*, 1950, 2904) indicated that two other hydrocarbons might be 10 : 11-benzofluoranthene. von Braun and Kirschbaum (*Ber.*, 1921, **54**, 597) by the action of sulphuric acid on 1 : 2-dihydronaphthalene obtained a product, $C_{20}H_{20}$, which on dehydrogenation gave a hydrocarbon, $C_{20}H_{12}$. Dansi and Ferri (*loc. cit.*) by the action of aluminium chloride on tetralin obtained a substance $C_{20}H_{20}$, which on dehydrogenation gave a hydrocarbon, $C_{20}H_{12}$, identical with that of the German workers (Dansi and Reggiani, *Gazzetta*, 1948, **78**, 801). We have repeated the work of von Braun and Kirschbaum and have found their final product to be identical with 10 : 11-benzofluoranthene. It follows that the hydrocarbon of the Italian workers is likewise 10 : 11-benzofluoranthene. The statement by Bell and Hunter (*loc. cit.*) " that a true dinaphthylene has still to be described " is thereby confirmed. Further since we effected dehydrogenation under mild conditions (chloranil in boiling xylene) von Braun and Kirschbaum's compound $C_{20}H_{20}$ must be an octahydro-10 : 11-benzofluoranthene, and we suggest it is probably 1 : 2 : 3 : 4 : 9 : 12 : 13 : 14-octahydro-10 : 11-benzofluoranthene (VI). Polarisation of the ethylenic double bond in 1 : 2-dihydronaphthalene will give $-\overset{\oplus}{\underset{(1)}{C}}H-\overset{\ominus}{\underset{(2)}{C}}H-$ which will combine with a proton to form a carbonium ion $-\overset{\oplus}{\underset{(1)}{C}}H-\underset{(2)}{C}H_2-$. Interaction of the carbonium ion and the polar compound will afford the dimeric carbonium ion (IV) (cf. Whitmore, *Ind. Eng. Chem.*, 1934, **26**, 94). Passage of (IV) into the octahydrobenzofluoranthene is more open to debate and might be effected by direct attack by the positive centre followed by elimination of a proton, or a proton might first be lost to give the unsaturated hydrocarbon (V). Ring closure would then result from the action of the sulphuric acid on the double bond, followed by interaction with the other " half " of the molecule. If the second alternative is indeed the mode of action it would add to the very few known instances of vinyl compounds undergoing cycloisomerisation (Bergmann,

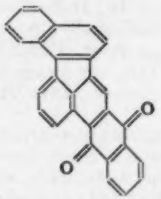
Chem. Reviews, 1941, **29**, 529; Cook and Lawrence, *J.*, 1936, 1431). The ultra-violet absorption spectrum of the octahydrobenzofluoranthene resembles that of tetralin and is thus in harmony with formula (VI) and clearly shows the absence of a double bond conjugated with a benzene ring.

(IV.)

(V.)



(VI.)



(VII.)

Heating 9-methyl-3 : 4-benzofluoren-9-ol with 1 : 4-naphthaquinone and acetic anhydride gives an adduct which is probably 10 : 11-benzonaphtho(2′ : 3′-3 : 4)fluoranthene-1′ : 4′-quinone (VII). It is assumed that the ring-closure takes the same course as outlined above and does not involve the naphthalene part of the molecule.

We have dehydrogenated Schroeter's octahydroanthracene, m. p. 73—74° (*Ber.*, 1924, **57**, 1990), to anthracene.

Experimental.

All chromatographic experiments were done on alumina (Brockmann), and fluorescence observations were made with a Hanovia ultra-violet lamp. A Hilger medium quartz spectrophotometer was used for the spectroscopic measurements.

10 : 11-*Benzofluoranthene from* 1 : 2-*Dihydronaphthalene.*—Crude "bisdialin" (von Braun and Kirschbaum, *loc. cit*), b. p. 135—141°/0·03 mm., was further purified chromatographically with benzene as solvent and developer. A pale yellow viscous oil was obtained which on trituration with ethanol yielded 1 : 2 : 3 : 4 : 9 : 12 : 13 : 14-octahydro-10 : 11-benzofluoranthene, colourless crystals (from ethanol), m. p. 90—92° (lit., 93°) (Found : C, 92·3; H, 7·7. Calc. for $C_{20}H_{20}$: C, 92·3; H, 7·7%). Light absorption in *n*-hexane : Max. 268 (log ϵ = 3·08) and 277 mμ. (log ϵ = 3·13) and min. 245 (log ϵ = 2·58) and 273 mμ. (log ϵ = 2·98). The substance (1·0 g.) with chloranil (3·8 g.) in boiling sulphur-free xylene (20 ml.) (15 hours) (cf. Barclay and Campbell, *J.*, 1945, 530) was dehydrogenated to 10 : 11-benzofluoranthene, which after chromatographic purification crystallised from ethanol in yellow needles, m. p. 162—163°, showing no depression when admixed with an authentic sample (see below) (Found : C, 94·7; H, 5·0. Calc. for $C_{20}H_{12}$: C, 95·2; H, 4·8). The ultra-violet absorption spectrum in *n*-hexane closely resembles that obtained by Orchin and Reggel (*loc. cit.*, 1947) and Dansi and Reggiani (*loc. cit.*). 10 : 11-Benzofluoranthene forms a picrate, orange-red needles m. p. 190—192°, and a *s*-trinitrobenzene derivative, orange needles (from ethanol), m. p. 216—218° (lit., 219·8—220·5°).

Synthesis of 10 : 11-*Benzofluoranthene.*—9-Methyl-3 : 4-benzofluoren-9-ol (1·0 g.), maleic anhydride (3·0 g.), and acetic anhydride (10 ml.) were boiled for 4 hours. The cooled solution deposited 10 : 11-*benzofluoranthene*-3 : 4-*dicarboxylic anhydride* (0·2 g.) which crystallised from 1-methylnaphthalene in orange-red needles, m. p. > 330° (Found : C, 81·5; H, 2·9. $C_{22}H_{10}O_3$ requires C, 82·0; H, 3·1%). Failure to undergo decarboxylation when heated with alkaline potassium ferricyanide confirmed that the substance is fully aromatic (cf. Campbell and Gow, *J.*, 1949, 1555). The anhydride and methanol with sulphuric acid gave the *dimethyl* ester, yellow needles (from methanol–benzene), m. p. 203—204° (Found : C, 76·0; H, 4·7. $C_{24}H_{14}O_4,CH_3{\cdot}OH$ requires C, 75·0; H, 5·0%). The anhydride (100 mg.) was intimately mixed with a large excess of calcium oxide and strongly heated. The yellow sublimate which rapidly separated was chromatographed in benzene. Development with light petroleum (b. p. 100—120°) gave a yellow zone which yielded 10 : 11-benzofluoranthene (70 mg.), compact prisms (from light petroleum), m. p. 163—164° (Found : C, 94·5; H, 5·1. Calc. for $C_{20}H_{12}$: C, 95·2; H, 4·8%). The substance in solution shows a bright green fluorescence and gives in warm concentrated sulphuric acid an olive-green solution.

10 : 11-*Benzonaphtho*(2′ : 3′-3 : 4)*fluoranthene*-1′ : 4′-*quinone.*—9-Methyl-3 : 4-benzofluoren-9-ol (1·0 g.), 1 : 4-naphthaquinone (4 g.), and acetic anhydride (20 ml.) were boiled for 2 hours. The *adduct* (50 mg.) separated and on sublimation gave scarlet prisms, m. p. >330° (Found : C, 87·5; H, 3·9. $C_{28}H_{14}O_3$ requires C, 87·5; H, 3·7%). It gives a greenish-brown colour with concentrated sulphuric acid and a deep blue vat with alkaline dithionite (hydrosulphite).

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University of Edinburgh. [*Received, June 8th*, 1951.]

558. *An All-glass Calorimeter, and the Heat of Combustion of Ethyl Chloride.*

By D. W. H. Casey and S. Fordham.

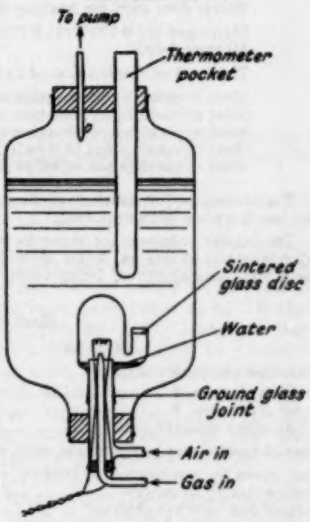
An all-glass calorimeter is described, suitable for determination of the heats of combustion of gases containing halogens. The heat of combustion of ethyl chloride vapour was determined as 341 ± 2·5 kcals./g.-mol. at 20°.

The work described below was started because engineering calculations required a value of the heat of combustion of ethyl chloride accurate to about 2 kcals./g.-mol. The first attempts at measurement were made with a bomb calorimeter, the ethyl chloride being sealed under low pressure into containers made first of glass and later of Polythene. These experiments were terminated when corrosion of the bomb by hydrochloric acid was observed. Trials were then made with a combustion calorimeter, but ignition was difficult and combustion incomplete, and on one occasion a gas explosion occurred. It was then decided to design an all-glass calorimeter for further measurements.

Experimental.

All-glass Calorimeter.—The principle adopted was to burn the gas in a stream of air or oxygen and bubble the products directly through water in the calorimeter. The apparatus is illustrated in the figure. The calorimeter vessel of glass was separated from a copper jacket by a 1-cm. air gap, and the whole was immersed in a thermostat at 20°. All gases were brought to 20° before being introduced into the calorimeter.

Glass Calorimeter.



Gas to be burnt was displaced from the storage vessel by a steady stream of mercury, and passed through capillary tubing to a hard-glass combustion jet. Air or oxygen for combustion was drawn through the apparatus by suction and was introduced saturated with water at 20° at a steady rate observed on a flowmeter between the calorimeter and the pump. Attempts to employ spark ignition were unsuccessful and a platinum-wire spiral was used, the energy dissipated being kept independent of the temperature of the wire to a first approximation, by electrical heating from accumulators, with a total circuit resistance equal to twice that of the spiral.

The combustion chamber had a short vertical side arm, closed at the top by a sintered glass disc. Ingress of the water in which the chamber was immersed was prevented by coating the sintered glass lightly with Apiezon M grease from benzene solution. The bottom of the combustion chamber was shaped to hold about 5 c.c. of water, and in practice about 2 c.c. were introduced before the beginning of any combustion involving chlorides so as to ensure adequate dilution of any aqueous hydrochloric acid condensate.

Temperatures were measured in early experiments with a Beckmann thermometer to ±0·001° and later to a higher accuracy with a platinum resistance thermometer and a Smith difference bridge. Temperature rises were derived graphically in the usual way and were of the order of 1°. Calibration was effected by burning known volumes (about 160 c.c.) of pure hydrogen, prepared from pure zinc and hydrochloric acid and washed and dried before use. The calorimeter held about 500 c.c. of water, the total water equivalent after filling being about 600 g.

In calculation of the results, the major allowance necessary is for the heat set free in the platinum spiral, which was kept hot during all combustion. This allowance was determined separately for each experiment. It accounted for nearly 30% of the observed temperature rises in most experiments but did not constitute a source of error as it could be measured accurately. A correction was made for the gas which remained unburnt in the capillary connection between the reservoir and the jet, and a further small correction was also made for the water vapour condensed from the oxygen used in combustion of hydrogen.

Difficulty was sometimes experienced in maintaining combustion of gases containing halogens, even after dilution with hydrogen. This was cured empirically when necessary by adjusting the jet size and gas velocity. Under the conditions described above and in the latter portion of this paper, the accuracy achieved in the measurement of heat liberated was considered to be approximately ±0·5%.

Heat of Combustion of Ethyl Chloride.—To ensure adequate combustion without liberation of free halogen, ethyl chloride was burnt as a dry mixture containing 90% by volume of hydrogen. The

proportions of gases needed were measured by volume, the ethyl chloride used having been purified by repeated distillation, and the hydrogen having been prepared from zinc and hydrochloric acid.

The procedure adopted was the following. The calorimeter was set up, air flow was adjusted, and conditions were allowed to become stable. From then on temperature readings were taken at suitable regular intervals, usually of 1 minute. First the correction due to the ignition coil was determined by passing the current for a known period. Then the calorimeter was standardised by burning a known volume of hydrogen, the ignition coil being kept hot for a known period, longer than the actual combustion. The hydrogen and ethyl chloride were then burnt in a similar manner. It was then usual to repeat the standardisation with hydrogen and the determination of the correction due to the ignition coil.

The gases from the combustion were tested for carbon monoxide, and the water in the calorimeter was tested for hypochlorite, but in no case was a positive result obtained.

The following data for a single run illustrate the results obtained and the method of calculation :

Vol. of hydrogen for standardisation		158 ml. at 16°/781 mm.
Mixture for combustion	ethyl chloride	16·2 ml. ,,
	hydrogen	138·8 ml. ,,

(The above volumes are corrected for gas unburnt in the leads.)

Standardisation of calorimeter :

(1) Temp. rise 1·176°; duration of heating of ignition coil 140 sec.
(2) ,, 1·249°; ,, ,, ,, 165 sec.

Heating effect of ignition coil 0·174°/min.

Combustion of ethyl chloride–hydrogen mixture :

Temp. rise 1·480°; duration of heating of ignition coil 135 sec.

Temp. rise, corr. for heating of ignition coil :

Hydrogen (1) 0·770°, (2) 0·771°.
Mixture 1·088°.

The heat of combustion of hydrogen was taken to be 68·38 kcals./g.-mol.

Heat evolved by combustion of hydrogen for standardisation	= 468·2 cals.
Heat evolved by combustion of mixture	= 661·6 ,,
Heat evolved by combustion of hydrogen in mixture	= 411·0 ,,
Heat of combustion of 0·0470 g. of ethyl chloride	= 250·6 ,,
Heat of combustion of ethyl chloride	= 343 cals./g.-mol.

The correction for moisture condensed from oxygen used in combustion amounts to less than 0·1% and has therefore been neglected.

The results obtained are given in the table. The mean value of the heat of combustion of ethyl chloride obtained was 341 kcals./g.-mol. and, on the assumption that there is no systematic error, this has a 95% probability of being within ±2·5 of the true value. This figure relates to gaseous ethyl

Heat of combustion of ethyl chloride.

Expt. no. :	I	II	III	IV
Corrected temperature rises :				
(i) hydrogen, 1	0·774°	0·770°	0·769°	0·880°
(ii) hydrogen, 2	0·774°	0·771°	—	0·869°
(iii) ethyl chloride mixture	1·086°	1·088°	1·215°	1·197°
Heat of combustion of hydrogen used, cals.	470·1	468·2	470·7	448·7
Heat given by combustion of mixture, cals.	660	662	744	614
Portion due to hydrogen	412	411	394	398
Portion due to ethyl chloride	248	251	350	216
Mass of ethyl chloride combusted, g.	0·0472	0·0470	0·0660	0·0409
Heat of combustion of ethyl chloride, kcals./g.-mol.	338	343	342	341

chloride at 20° with products of combustion carbon dioxide (g.), hydrochloric acid (dil. aq.), and liquid water. The corresponding heat of formation of the gas is 24 kcals./g.-mol., if the heat of formation of carbon dioxide is assumed to be 94·38 kcals./g.-mol. and that of dilute aqueous hydrochloric acid 39·46 kcals./g.-mol.

Discussion.

The following figures have been converted when necessary to gaseous ethyl chloride at 20°, the products of combustion being gaseous carbon dioxide, dilute aqueous hydrochloric acid, and liquid water.

Berthelot ("Essai de Mechanique Chimique," Dunos, Paris, 1879, p. 107) and Thomsen

(" Thermochemistry," Longmans Green, 1908, p. 370) measured the heat of combustion of ethyl chloride directly and obtained values of 334 and 326 kcals./g.-mol. respectively. Rudkowski, Trifel, and Frost (*Uhrain. Chem. J.*, 1935, **10**, 277) studied the equilibrium $C_2H_4 + HCl \rightleftharpoons C_2H_5Cl$ in the temperature range 170—230° and their values for the equilibrium constant give a mean heat of reaction in this temperature range of 13·4 kcals. This was converted to 20° by means of known specific-heat data and used in conjunction with the heat of formation of ethylene given by Rossini and Prosen (*J. Res. Nat. Bur. Stand.*, 1946, **36**, 269). The heat of combustion of ethyl chloride thus determined was 342 kcals./g.-mol.

Less direct estimates of the heat of combustion of ethyl chloride may be obtained from bond-energy data. The energy of the C–Cl bond is, for example, often derived from results with compounds such as methyl chloride containing a single C–Cl bond and these values may be used directly, provided that care is taken to avoid confusion owing to the assumption of different heats of sublimation of graphite (Long and Norrish, *Proc. Roy. Soc.*, 1946, *A*, **187**, 337). In order to limit errors as far as possible, the heat of formation of ethane given by Bichowsky and Rossini (" The Thermochemistry of Chemical Substances," Rheinhold, 1936) has been adopted (21 kcals./g.-mol.), so that only the difference in the energies of the C–Cl and C–H bonds needs to be used, together with the heats of dissociation of hydrogen and chlorine. The following scheme represents the method, bond energies being represented by Q and dissociation energies by D.

$$2C_2H_5Cl = 2C_2H_5 + 2Cl - 2Q_{CCl}$$

$$2Cl = Cl_2 + D_{Cl_2}$$

Therefore,
$$2C_2H_5Cl = 2C_2H_5 + Cl_2 - 2Q_{CCl} + D_{Cl_2}$$

$$H_2 = 2H - D_{H_2}$$

$$2C_2H_5 + 2H = 2C_2H_6 + 2Q_{CH}$$

Therefore,
$$2C_2H_5 + H_2 = 2C_2H_6 + 2Q_{CH} - D_{H_2}$$

Therefore,
$$2C_2H_5Cl + H_2 = 2C_2H_6 + Cl_2 + 2Q_{CH} - 2Q_{CCl} + D_{Cl_2} - D_{H_2}$$

The heat of formation thus deduced may be converted into the heat of combustion in the usual way. The heats of dissociation of chlorine and hydrogen were taken as 57·4 and 100·8 respectively.

Pauling (" Nature of the Chemical Bond," Cornell, 2nd Edn., 1944, p. 53) gives the mean energies of the C–Cl and C–H bonds as 66·5 and 87·3 kcals. respectively, from which the heat of combustion may be calculated as 343 kcals./g.-mol. (a complete summation of the molecules using Pauling's values for bond energies and dissociation energies gives 339 kcals./g.-mol.). A further approach is possible along the lines indicated by Barton and Howlett (*J.*, 1949, 155). The heat of addition of chlorine to ethylene at 355° K. has been determined as 43·7 kcals. by Conn, Kistiakowsky, and Smith (*J. Amer. Chem. Soc.*, 1938, **60**, 2764), corresponding to 43·9 kcals. at 20°. The heat of hydrogenation of ethylene has been measured by Conant and Kistiakowsky (*Chem. Reviews*, 1937, **20**, 181) as 32·8 kcals./g.-mol. The corresponding difference between the energies of the C–Cl and C–H bonds is 16·2 kcals., the above heats of dissociation being assumed, and this leads to a heat of combustion of ethyl chloride of 338 kcals./g.-mol. A direct deduction from the figures given by Bichowsky and Rossini (*op. cit.*) for methane, methyl chloride, and ethane gives a heat of combustion for ethyl chloride of 342 kcals./g.-mol.

The results of the present work do not agree with the earlier direct measurements by Berthelot and Thomsen, but do agree with the work of Rudkowski, Trifel, and Frost on the equilibrium between ethylene and gaseous hydrogen chloride. The agreement with the mean bond energies deduced by Pauling is also satisfactory, although these may not in fact have been deduced from compounds of type relevant to the present work. The agreement between the methyl and the ethyl system is also satisfactory.

It is interesting to note that the heat of combustion of ethyl chloride determined in this work differs somewhat from that deduced above from the heats of hydrogenation and chlorination of ethylene. Conn, Kistiakowsky, and Smith (*loc. cit.*) have discussed this in a different way, by calculating from their data the heat of hydrochlorination of ethylene. They deduce 15·9 kcals. at 25°, whereas they calculate 14·6 kcals. from the heat of formation of ethyl chloride, quoted by Bichowsky and Rossini (*op. cit.*) as 25·7 kcals./g.-mol. (the origin of this figure is not stated by Bichowsky and Rossini, and a literature search failed to reveal determinations other than those given above). By use of the present value for the heat of formation of ethyl chloride,

the heat of hydrochlorination is calculated to be 13 kcals., other thermochemical data used being unchanged. The energy of the C–Cl bond in ethyl chloride is thus about 3 kcals. less than the mean C–Cl bond energy in ethylene dichloride, a rather unexpected result which suggests that the configuration of the latter compound is rather more favourable to stability than is that of the former. The difference is, however, on the borderline of experimental accuracy.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, NOBEL DIVISION,
RESEARCH DEPARTMENT, STEVENSTON. [*Received, February 9th*, 1951.]

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559. *Solutions of Alcohols in Non-polar Solvents. Part I. The Solubility and Heat of Solution of Water in Dilute Solutions of Alcohols in Benzene.*

By L. A. K. STAVELEY, R. G. S. JOHNS, and B. C. MOORE.

The solubility of water in dilute solutions of methanol, ethanol, *n*-butanol, *n*-pentanol, and *n*-octanol in benzene has been determined by the synthetic method over a range of temperature. An apparatus is described with which the three components can be introduced into a tube so that the amount of each is known with considerable precision, even though that of the water is very small. The molar heat of solution of water ΔH has been evaluated from the solubility results. Whereas ΔH for benzene solutions of pentanol and octanol decreases with increasing alcohol concentration, with butanol solutions ΔH first rises slightly before undergoing a fairly rapid fall. This peculiar course of ΔH at low alcohol concentrations is ascribed to an interaction between the alcoholic hydroxyl group and the polarisable benzene molecules which in turn affects that between the water and benzene. It is suggested that the reason for the different behaviour of the pentanol and octanol solutions is that the molecules of these alcohols tend to adopt a coiled configuration in benzene, whereby the hydroxyl group is partly screened. For dilute solutions of butanol, pentanol, and octanol in benzene, there is a linear relation between the heat and entropy of solution of water.

IN a previous paper (Staveley, Jeffes, and Moy, *Trans. Faraday Soc.*, 1943, **39**, 5) some measurements of the solubility of water in benzene containing organic substances of various chemical types were reported. These measurements were intended to throw light on the interaction between molecules of water and those of the organic substances. It seemed that a useful extension of this work would be to examine in greater detail the solubility of water in benzene solutions of substances such as simple alcohols with which water molecules interact particularly strongly. Previous studies of three-component systems involving water, an alcohol, and a non-polar solvent have usually been carried out at one temperature only, and in any case have not been sufficiently detailed at low alcohol concentrations to give any information about the interaction of *monomeric* alcohol and water molecules.

From measurements of the solubility of water in a given medium over a range of temperature an estimate can be made of ΔH, the heat of solution of water. (The basis of this calculation will be discussed more fully later.) Before the experiments were commenced, it was expected that the addition of alcohol to benzene would decrease ΔH, owing to the exothermic interaction of water and alcohol molecules, and it was hoped to estimate the heat of this interaction from the experimental curve relating ΔH and alcohol concentration. Experiments were therefore carried out on the solubility of water in benzene solutions of methanol and ethanol, using the simple technique employed in the earlier work. (This consists in sealing within a tube a small known amount of water with a known amount of the organic medium, heating the tube until the contents become homogeneous, and then finding the temperature at which the aqueous phase appears on cooling). The results were surprising, in that, as the alcohol concentration increased from zero, ΔH did not at first show its expected fall, but instead remained almost constant or even rose slightly to a maximum value, after which there was a rapid drop. One objection to these experiments, however, was that the aqueous phase which separates from even very dilute solutions of methanol or ethanol in benzene is not pure water, but contains considerable quantities of the alcohol. It was therefore considered desirable to carry out

further experiments with higher alcohols, and this was done with *n*-butanol, *n*-pentanol, and *n*-octanol.

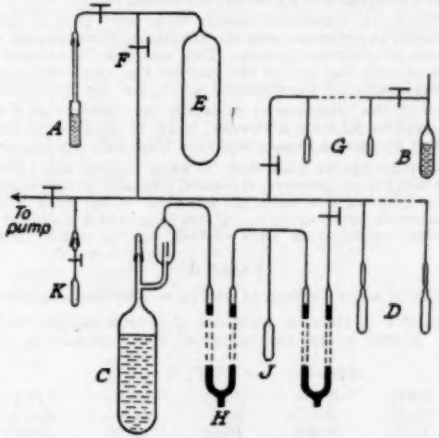
Values for the solubility of water in benzene have recently been obtained by Joris and Taylor (*J. Chem. Physics*, 1948, **16**, 45) using tritium. These are considerably lower than those obtained by both synthetic and analytical methods, and Joris and Taylor suggest possible reasons why the latter methods might lead to erroneously high values. It seems curious, however, that their value for the solubility of water in benzene at 20° is even lower than the concentration of water in benzene in equilibrium with the salts Na_2SO_4 and $Na_2SO_4.10H_2O$. In the determination of the latter quantity (Bell, *J.*, 1932, 2903) the analytical method used had been very carefully tested, and interference from colloidally dispersed water (which Joris and Taylor suggest as a possible source of error in the synthetic method) can scarcely arise. It seems to us that it cannot be regarded as proven that the synthetic method does not give reliable results when applied to systems of this kind.

Experimental.

Any one solubility determination involved making up a mixture of known amounts of water, benzene, and the alcohol in a sealed tube, heating this until it became homogeneous, and then determining the temperature at which the system separated into two phases on cooling. This temperature could be determined to 0·1—0·2°. In the experiments on methanol and ethanol, the water was added from a weight pipette. The risk of loss by evaporation during this operation, the possibility of the benzene–alcohol mixture picking up atmospheric moisture during the transference of this mixture into the tube, and the fact that the quantities of water involved were very small, combined to make uncertainty in the exact mass of water sealed within a tube the chief source of experimental error.

Fig. 1.

Apparatus for filling tubes with known amounts of water, benzene, and an alcohol.



For the experiments on butanol and pentanol an improved technique was therefore adopted. All three components were manipulated in a closed apparatus and introduced into a tube by condensation in such a way that the amount of each was accurately known. For octanol, which is comparatively involatile, this method was used in a modified form, as described later.

Fig. 1 shows the main features of the apparatus used in the experiments with butanol and pentanol. The water was contained in the small copper vessel *A*, the alcohol in *B*, and the benzene in *C*. Each liquid was degassed by repeated freezing, evacuation, and melting. The tubes *D* into which the three substances were condensed were provided with constrictions at which they were eventually sealed off. The volume of each tube up to the mid-point of the constriction was determined in advance, and was ~30 c.c.

The volume of the vessel *E* (~470 c.c.) was such that when it was filled with water vapour at the vapour pressure of water at ~12°, the amount of water in it was the minimum required for any one of the tubes *D*. The actual quantity of water contained in *E* for a known pressure and with *E* at a known temperature (~25°) was found as follows: *A* was surrounded by water in a Dewar vessel and its temperature kept constant somewhere between 11·5° and 12·5°. After *E* had been evacuated, it was put in communication with the water in *A*. The temperature of *A* was read to 0·01°, and that of the bath surrounding *E* to 0·1°, and the communicating tap closed. By opening tap *F*, the vapour in *E* was condensed into the detachable trap *K*, which was cooled in liquid air. A period of 8 minutes was

allowed for this condensation, this being more than sufficient for the pressure to fall below the minimum necessary for the production of a glow in a discharge tube. At the end of this time, F was closed and the whole process repeated until it had been carried out twenty times in all. The trap K, which now contained about 0·1 g. of water, was detached and weighed. The mass of water in E at each filling was then calculated on the assumption that the water vapour obeyed the perfect-gas laws, its pressure being the water vapour pressure at the temperature of A during the filling. The actual mass of water in the trap proved to be 1·014 times that obtained by summing the calculated values for each of the twenty fillings. Two repetitions of this calibration exeriment, also of twenty fillings each, gave exactly the same numerical factor. In preliminary experiments, it had been found that if the temperature difference between A and E was only 2—3°, the numerical factor was much larger and no longer reproducible, presumably owing to adsorption effects becoming considerable when the pressure of the vapour in E was only slightly less than the water vapour pressure at the temperature of E (cf. McHaffie and Lenher, *J.*, 1925, **127**, 1559). In introducing water into the tubes D in the same way, the temperatures of A and E were kept between the same limits as during the calibration experiments, and the sum of the calculated quantities of water for each filling was multiplied by the factor 1·014 to give the mass actually condensed into the tube. The number of fillings of E for any one tube D was of course chosen to give as nearly as possible the required total amount of water.

The capacities of the six small vessels G, of which two are shown, varied from 0·19 to 2·5 c.c. Each had a capillary inlet, and had been accurately calibrated at 0° to a mark on the capillary. In filling the tubes D for determinations of the solubility of water in a particular solution of an alcohol in benzene, the same vessel G was of course used throughout. Alcohol was condensed into it up to the calibration mark while it was surrounded by melting ice. The contents of the vessel were then condensed into the tube D.

Benzene was stored over phosphoric oxide in the vessel C. A mercury cut-off H separated it from a calibrated vessel J, the volume of which to a mark on the stem (~23 c.c.) had been found at a temperature just above the m. p. of benzene. J was maintained at this temperature when it was filled with benzene by evaporation from C, and this charge of benzene was then condensed into a tube D. The order of admission of the three substances into a tube was water, alcohol, benzene. The tube was finally cooled in liquid air and sealed off at the constriction. It is considered that the errors in the amounts of each of the three substances in a tube did not exceed 0·2%.

Octanol is too involatile to be transferred readily from one vessel to another by evaporation at ordinary temperatures. In the experiments with this substance, therefore, the required amount of water was introduced into a tube as described above. This was then filled with dry air to atmospheric pressure, and while still very cold was cut off the vacuum line above the constriction. The required amount of the octanol–benzene solution was siphoned into it, and the tube sealed off.

Accurate determination of the temperature at which the contents of a tube separated into two phases on cooling was assisted by focusing a powerful beam of light on the tube at right angles to the direction of observation, and by using a comparison tube filled with dry benzene.

Since it is known that considerable quantities of water vapour are adsorbed on glass when the pressure is near the saturation vapour pressure, it seemed desirable to investigate the possibility that as a tube is cooled appreciable quantities of water are adsorbed on the walls in the neighbourhood of the temperature at which the aqueous phase appears. If this happened it might, of course, introduce serious errors. Accordingly, several experiments were carried out in which, after the critical solution

TABLE I.

Solubility of water in benzene and in alcohol–benzene mixtures.

The solubility of water at $t°$ is given as N, where N = mole-fraction of water × 10^3; N_A is the mole-fraction of alcohol; a and b are the values of the constants in the equation $\log_{10} N = a - 10^3 b/(t + 273{\cdot}1)$.

Benzene: $a = 5{\cdot}237$; $b = 1{\cdot}427$.

N	2·606	3·674	3·784	5·041	5·153	6·064	6·902	7·078
t	22·7°	30·5°	33·0°	40·6°	41·9°	45·9°	51·9°	52·2°
N	7·211	7·521	9·294	10·50	11·21	13·02		
t	53·2°	54·7°	60·9°	65·3°	67·2°	73·2°		

Methanol–benzene.

$N_A = 0{\cdot}0113$; $a = 5{\cdot}219$, $b = 1{\cdot}416$.

N	3·07	3·96	4·62	6·18	9·455
t	26·0°	33·5°	37·7°	46·1°	60·1°

$N_A = 0{\cdot}0226$; $a = 5{\cdot}339$, $b = 1{\cdot}430$.

N	2·88	4·51	6·21	8·87	9·80
t	20·0°	32·4°	42·0°	49·8°	56·4°

$N_A = 0{\cdot}0332$; $a = 5{\cdot}158$, $b = 1{\cdot}370$.

N	4·15	5·08	6·08	7·77	10·18
t	28·7°	34·5°	40·1°	47·9°	56·5°

$N_A = 0{\cdot}04125$; $a = 5{\cdot}217$, $b = 1{\cdot}385$.

N	4·26	4·675	7·375	9·07	12·23
t	28·4°	32·2°	44·6°	52·0°	62·8°

$N_A = 0{\cdot}0458$; $a = 4{\cdot}935$, $b = 1{\cdot}277$.

N	4·07	7·44	9·17	14·11	15·09
t	22·5°	41·1°	47·4°	64·1°	67·6°

$N_A = 0{\cdot}0568$; $a = 4{\cdot}358$, $b = 1{\cdot}055$.

N	6·41	7·89	9·31	11·71	12·51
t	23·7°	31·6°	37·9°	47·8°	50·7°

$N_A = 0{\cdot}0781$; $a = 3{\cdot}704$, $b = 0{\cdot}8208$.

N	8·28	10·63	13·48	15·31	18·16
t	22·2°	32·7°	46·2°	53·1°	61·6°

$N_A = 0{\cdot}1047$; $a = 3{\cdot}594$, $b = 0{\cdot}7539$.

N	9·44	10·82	14·63	16·45	
t	15·0°	22·2°	35·6°	43·7°	

TABLE I.—(*continued*).

Ethanol–benzene.

$N_A = 0.00644$; $a = 5.638$, $b = 1.547$.

N	3·12	3·96	5·29	8·02	8·51	12·19
t	27·2°	34·4°	42·2°	53·7°	55·2°	66·5°

$N_A = 0.0143$; $a = 5.758$, $b = 1.571$.

N	2·01	4·10	5·02	6·97	8·32	14·28
t	14·7°	32·6°	37·4°	46·4°	51·6°	68·7°

$N_A = 0.0183$; $a = 5.341$, $b = 1.436$.

N	3·42	5·555	6·91	8·27	10·87	13·06
t	26·1°	39·1°	45·4°	51·6°	60·6°	67·7°

$N_A = 0.02465$; $a = 4.238$, $b = 1.070$.

N	3·58	4·19	4·68	5·57	7·10	9·59	11·26	12·75
t	18·7°	23·1°	26·6°	32·1°	41·6°	57·3°	61·7°	68·4°

$N_A = 0.02986$; $a = 3.323$, $b = 0.757$.

N	4·71	7·01	8·38	10·53
t	16·7°	32·3°	43·4°	55·6°

$N_A = 0.0563$; $a = 3.560$, $b = 0.765$.

N	5·89	7·75	10·13	14·77
t	1·3°	12·2°	27·5°	48·6°

$N_A = 0.04213$; $a = 3.397$, $b = 0.749$.

N	5·96	8·27	9·62	9·70	10·04	14·62
t	11·5°	27·9°	38·6°	38·8°	39·0°	62·1°

$N_A = 0.0691$; $a = 3.426$, $b = 0.702$.

N	9·30	11·12	13·57	16·60	19·43
t	13·0°	21·4°	32·6°	41·6°	56·5°

Butanol–benzene.

$N_A = 0.00802$; $a = 5.342$, $b = 1.439$.

N	3·272	4·345	6·027	8·224
t	24·7°	32·6°	42·3°	51·5°

$N_A = 0.0329$; $a = 3.121$, $b = 0.681$.

N	5·755	7·082	8·065	9·745	11·80
t	14·8°	26·4°	34·3°	45·9°	57·9°

$N_A = 0.01405$; $a = 4.745$, $b = 1.221$.

N	3·366	6·209	8·056	10·38
t	16·8°	35·6°	45·1°	54·2°

$N_A = 0.0561$; $a = 2.807$, $b = 0.545$.

N	7·949	9·380	11·01	12·67	14·67
t	12·6°	24·1°	35·9°	47·2°	60·2°

$N_A = 0.02615$; $a = 3.585$, $b = 0.845$.

N	4·665	5·746	6·968	8·511	10·27
t	18·8°	26·8°	35·0°	44·0°	51·9°

$N_A = 0.0973$; $a = 2.763$, $b = 0.479$.

N	12·30	14·19	16·25	18·37	20·97
t	13·8°	24·3°	35·6°	46·8°	59·5°

Pentanol–benzene.

$N_A = 0.00698$; $a = 4.948$, $b = 1.310$.

N	2·690	3·803	5·429	7·418	10·01
t	17·2°	27·8°	38·0°	48·2°	57·8°

$N_A = 0.0119$; $a = 4.780$, $b = 1.238$.

N	2·926	3·394	3·927	5·095	5·928	7·063	9·036	11·08
t	12·8°	17·9°	22·7°	31·7°	36·3°	41·9°	49·6°	56·7°

$N_A = 0.0223$; $a = 4.292$, $b = 1.076$.

N	3·803	3·837	4·839	5·794	6·798	6·947	8·802	11·58
t	15·0°	15·4°	23·2°	30·4°	37·6°	37·9°	47·3°	58·3°

$N_A = 0.0281$; $a = 2.838$, $b = 0.603$.

N	5·766	5·853	6·968	7·841	8·851	9·851
t	16·7°	17·4°	29·0°	37·4°	45·0°	51·8°

$N_A = 0.0486$; $a = 2.771$, $b = 0.546$.

N	7·814	9·414	11·21	12·75	14·94
t	18·1°	31·2°	43·1°	52·0°	68·0°

$N_A = 0.08425$; $a = 2.733$, $b = 0.480$.

N	10·79	13·52	16·09	18·90
t	11·2°	28·4°	43·3°	57·8°

Octanol–benzene.

$N_A = 0.0166$; $a = 4.613$, $b = 1.231$.

N	2·735	3·735	4·355	6·284	8·556
t	22·5°	31·0°	33·0°	49·5°	62·1°

$N_A = 0.0314$; $a = 4.137$, $b = 1.030$.

N	3·593	4·521	5·352	7·200
t	14·3°	23·7°	28·4°	41·65°

$N_A = 0.0435$; $a = 4.217$, $b = 1.037$.

N	5·699	6·621	7·258	7·952	9·348	11·05
t	26·0°	33·5°	35·8°	38·9°	46·7°	53·4°

temperature for a tube had been determined, the tube was warmed to a slightly higher temperature, opened, and the major part of its contents blown over into another dry tube. This was then sealed and used for another determination of the critical solution temperature. This temperature was always identical within the limits of experimental error (±0·2°) with that obtained with the first tube.

Benzene was chemically purified by the method of Richards and Shipley (*J. Amer. Chem. Soc.*, 1914, **36**, 1825; 1919, **41**, 2007), and then submitted to fractional crystallisation, or distillation, or both. It was finally dried over resublimed phosphoric anhydride. The alcohols were purified by fractional distillation, the butanol being first subjected to the chemical treatment described by Weissberger and Proskauer ("Organic Solvents," Oxford, 1935). They were dried first by refluxing them over freshly-ignited lime, and finally by means of aluminium amalgam (for butanol, pentanol, and octanol), or with magnesium (for methanol and ethanol).

Results.—In every solubility determination, a correction was applied for the amount of water present in the vapour phase in the tube. Values for the solubility of water in benzene and in various solutions in benzene of the five alcohols studied are recorded in Table I; N is the millimole-fraction of the water in a saturated solution at $t°$. In a series of experiments with solutions containing a fixed alcohol : benzene ratio, the mole-fraction of alcohol in the water-saturated solution decreases slightly as the temperature rises, owing to the increased solubility of water. As the change seldom exceeds 0·5%, the concentration of the alcohol in any one series has been given in Table I as a mean mole-fraction, N_A.

FIG. 2.

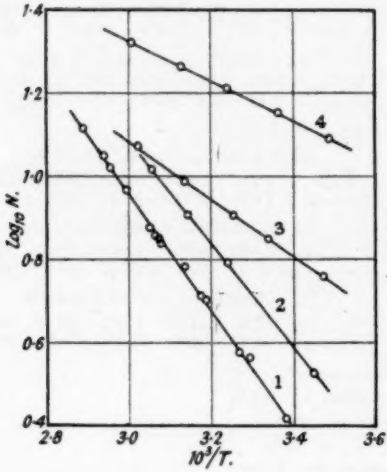


FIG. 3.

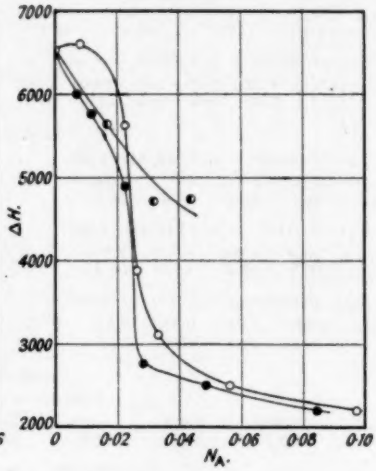


FIG. 2.

Specimen plots of $\log_{10}$ N *against* $10^3/T$ *for benzene and butanol–benzene mixtures.* (N *is the mole-fraction of water* × 10^3, *and* T *the absolute temperature*). *Line* 1 *is for benzene, and lines* 2, 3, *and* 4 *for butanol–benzene solutions containing the alcohol at mean mole-fractions of* 0·01405, 0·0329, *and* 0·0973, *respectively.*

FIG. 3.

Plots of ΔH (*in cals./mole, as calculated from equation* 2) *against* N_A, *the mole-fraction of alcohol, for butanol* (*open circles*), *pentanol* (*full circles*), *and octanol solutions* (*half-shaded circles*).

For benzene alone, and for every solution studied, log N is a linear function of $1/T$, where T is the absolute temperature. In Table I are recorded the values of a and b in the equation

$$\log_{10} N = a - 10^3 b/T$$

which were obtained from the experimental points by the method of least squares. How well this linear relation is obeyed is evident from Fig. 2, in which $\log_{10} N$ is plotted against $10^3/T$ for benzene alone and for several solutions of butanol in benzene.

DISCUSSION.

The temperature variation of the solubility of a non-ideal solute is governed by the exact equation

$$\Delta H = RT^2\left(\frac{dN}{dT}\right)_{sat.}\left[\left(\frac{\partial \ln f}{\partial N}\right)_T + \left(\frac{1}{N}\right)_{sat.}\right] \quad . \quad . \quad . \quad . \quad . \quad (1)$$

(cf. Williamson, *Trans. Faraday Soc.*, 1944, **40**, 421); ΔH is the heat absorbed when one mole

of solute dissolves in an infinite amount of the saturated solution, and f and N are respectively the activity coefficient and mole-fraction of the solute. For solutions of water in benzene, Peterson and Rodebush (*J. Physical Chem.*, 1928, **32**, 709) found that the freezing-point depression is a linear function of the water concentration, the water being unimolecular up to the saturation limit, and Greer (*J. Amer. Chem. Soc.*, 1930, **52**, 4191) observed that, at 20·9°, solutions of water in benzene obey Henry's law with considerable precision. We may therefore regard the water in solution in benzene as an ideal solute and neglect the first term in the square bracket of equation (1), which accordingly simplifies to

$$\Delta H = RT^2\left(\frac{\mathrm{d}\ln N}{\mathrm{d}T}\right)_{\mathrm{sat.}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

We shall suppose that equation (2) also applies to solutions of water in the mixtures of benzene and an alcohol. This assumes that the aqueous phase which separates from such mixtures is pure water, whereas it will in fact contain some of the alcohol. Some information about the composition of the aqueous phase can be obtained from the work of Butler and Harrower (*Trans. Faraday Soc.*, 1937, **33**, 171), who determined the limiting values of the distribution coefficients of the lower alcohols between water and benzene. From their figure for butanol, the mole-fraction of this alcohol in the aqueous phase in equilibrium with our most concentrated butanol–benzene solution should not exceed 0·028 at 25°, so the aqueous phase is at least 97·2 moles % water. Since, for the lower alcohols, the distribution coefficient rapidly increases with increasing molecular weight (in favour of concentration in the benzene), we may expect that for octanol and pentanol at the same concentration the water content of the aqueous phase is considerably nearer 100%. For the mixtures of benzene with butanol, pentanol, and octanol, the ΔH values recorded in Table II, which have been obtained by applying equation (2) to our solubility results, should therefore be very near the true values of the molar heat of solution of pure water. For methanol and ethanol the position is rather different. From Butler and Harrower's figures, the aqueous phase in equilibrium with a benzene solution containing one of these alcohols at a mole-fraction of only 0·01 is ~86 moles % water for methanol and ~95·5 for ethanol. Nevertheless, estimates of ΔH made by using equation (2) in the same way are also included in Table II, and it is noteworthy that they follow much the same course as those for the butanol solutions, in that, as the alcohol concentration increases from zero, ΔH first remains fairly constant, or even rises slightly, before undergoing a rapid fall.

TABLE II.

Values of ΔH, *in cals./mole, calculated from equation* (2) *for water in alcohol–benzene mixtures.*

[N_A is the mole-fraction of the alcohol. For water in benzene alone, ΔH = 6530.]

				Methanol–benzene.				
10^4N_A	113	226	332	412·5	458	568	781	1047
ΔH	6470	6540	6265	6330	5840	4825	3750	3450
				Ethanol–benzene.				
10^4N_A	64·4	143	183	246·5	298	421·3	563	691
ΔH	7040	7190	6570	4900	3465	3425	3500	3210
				Butanol–benzene.				
10^4N_A	80·2	140·5	261·5	329	561	973		
ΔH	6600	5585	3875	3120	2500	2200		
				Pentanol–benzene.				
10^4N_A	69·8	119	223	281	586	842·5		
ΔH	6000	5760	4900	2770	2500	2200		
				Octanol–benzene.				
10^4N_A	166	314	435					
ΔH	5630	4710	4740					

The systems water–methanol or ethanol–benzene could in principle be more satisfactorily treated from the standpoint of the distribution of water between the alcohol and benzene. With sufficiently accurate distribution data over a range of concentration and temperature, estimates could be made of the heat of transference of water from the alcohol to the benzene phase, which could be combined with values of the relative partial molar heat content of water in aqueous alcohol to give the required heats of solution. An attempt was made to do this for the water–ethanol–benzene system, using the distribution data of Tarassenkov and Poloshinzewa (*Ber.*, 1932, **65**, 184), and the results of Bose (*Z. physikal. Chem.*, 1907, **58**, 585) on the heats of

mixing of water and ethanol to give the partial molar heat contents. As the distribution data are not really comprehensive enough for the purpose, the presentation here of the modified figures obtained in this way does not seem justified. It may, however, be remarked that they do not differ by more than a few hundred calories from the ΔH values of Table II, and that they still rise slightly before falling rapidly to a fairly steady value. It therefore seems not unlikely that the variation with alcohol concentration of the true molar heat of solution of water in alcohol–benzene mixtures is much the same for methanol, ethanol, and butanol. But since there is less ambiguity in the ΔH values for solutions of butanol and the higher alcohols, the rest of the discussion will be confined to these systems, for which the variation of ΔH with alcohol concentration is shown graphically in Fig. 3.

Perhaps the most interesting feature of the experimental results is that for the butanol solutions ΔH first increases slightly as the alcohol concentration rises from zero, and does not start to fall rapidly until the mole-fraction of the alcohol is $\sim$0·02. For octanol and pentanol, ΔH decreases from the start. As the monomer of the alcohol is in equilibrium with alcohol polymers, the heat absorbed, ΔH, when one mole of water dissolves in an infinite amount of a water–alcohol–benzene mixture is a composite quantity, made up of the heat absorbed by that part of the water which dissolves as such, the heat effect due to the association of the remainder with alcohol molecules, and the heat effect consequent on the shift in the alcohol monomer–polymer equilibrium. At the relatively low alcohol concentrations under consideration, we may regard the association of the alcohol molecules as limited to the formation of the lowest polymer. From spectroscopic studies (Kreuzer and Mecke, *Z. physikal. Chem.*, 1941, *B*, **49**, 309; Hoffmann, *ibid.*, 1943, *B*, **53**, 179) this appears to be the trimer and not the dimer. For any values of the heats of association and of the equilibrium constant for the trimerisation of the alcohol which in the light of the spectroscopic work seem at all reasonable, calculation shows that ΔH decreases continuously as the alcohol concentration rises from zero. Presumably, therefore, other factors are responsible for the maximum in ΔH at low alcohol concentrations in the butanol–benzene mixtures. We consider that one, at least, of these may be the dipole–induced dipole interaction between the polar alcohol molecules and the polarisable benzene molecules. Wolf (*Trans. Faraday Soc.*, 1937, **33**, 179) found that the molar heat of solution of ethanol in benzene (for the production of a very dilute solution) is about 2000 cals. less than the corresponding figure for hexane and *cyclo*hexane. This suggests that in an alcohol–benzene mixture, each alcohol molecule is in rather close association with one or more solvent molecules, and it may be that this solvation of the alcohol molecules produces a salting-out effect in that the quantity of benzene unaffected by the presence of the alcohol and capable of dissolving water in the normal way is appreciably less than the total amount of benzene present. If this is so, it means that the activity coefficient of the water is altered by the presence of the alcohol, and that the application of the law of mass action in its ideal form even to the dilute solutions we have considered is not strictly valid. It may also be remarked that the solubility of water in benzene is appreciably higher than that in other non-polar solvents, and that the heat of solution of water in benzene is $\sim$1500 cals. less than that in petroleum, as assessed from Groschuff's solubility figures (*Z. Elektrochem.*, 1911, **17**, 348). These facts can likewise be attributed to dipole–induced dipole interaction between the water and benzene molecules. When water dissolves in the alcohol–benzene mixture it enters a medium in which some of the benzene molecules are already polarised by the alcohol, and it is possible that the dipole–induced dipole interaction energy between the water and benzene is reduced, so that effectively the heat of solution of that part of the water which dissolves as such is increased.

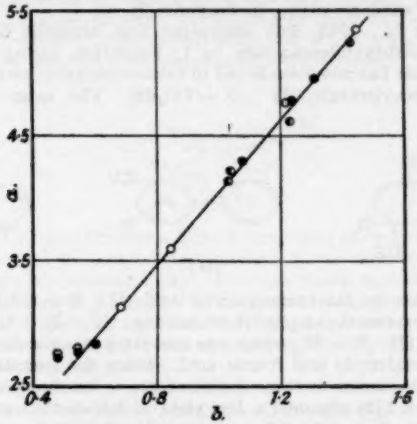
We may therefore, in general terms, tentatively attribute the peculiar course of the ΔH curve at low butanol concentrations to some sort of interaction between the hydroxyl group and the benzene which in turn affects the relationship between the benzene and the water. The simplest explanation of the fact that this abnormality in the trend of ΔH is less marked for benzene solutions of octanol and pentanol is that in these the hydroxyl group is in some way prevented from interacting so strongly with the neighbouring hydrocarbon molecules. This state of affairs would prevail if these alcohol molecules have a coiled configuration, so that the hydroxyl radical is to some extent screened by the alkyl group. It is possible that when flexible alcohol molecules are present in a solution at relatively low concentrations, they may tend to adapt themselves to conform to the geometry of the solvent molecules, so that stronger intermolecular attraction of the London kind and more economical molecular packing may be achieved. Girard and Abadie (*Discuss. Faraday Soc.*, 1946, **42**, *A*, 40) have in fact concluded from dispersion studies on octanol that in solution this molecule has the shape of an ellipsoid with three axes, whereas in the pure alcohol its shape is that of an ellipsoid of revolution.

The pentanol molecule, having five carbon atoms and one oxygen atom in a chain, could conceivably coil into a quasi-six-membered ring, the better to pack into the environment of hexagonal benzene molecules, and as a result the hydroxyl group would to some extent be screened, though not so completely as in coiled alcohol molecules with longer hydrocarbon chains. On this explanation, it would be expected that the differences observed in the ΔH curves for different alcohols in benzene would not necessarily arise with non-polar solvents the molecules of which are not cyclic. Thus, if a normal paraffin were used instead of benzene, higher alcohol molecules in solution in the paraffin might be encouraged to retain an open rather than a coiled configuration.

To test this conclusion, numerous attempts were made to measure the solubility of water in solutions of alcohols in hexane and in carbon tetrachloride, using the technique employed for

FIG. 4.

Showing the linear relation between the quantities a *and* b *in the equation* $\log_{10} N = a - 10^3 b/T$ *for the solubility of water in mixtures of benzene and butanol (open circles), pentanol (full circles), and octanol (half-shaded circles). The circle with the cross is the point for pure benzene.*



the benzene experiments. Nothing conclusive resulted from these experiments, however. They are made much more difficult with these two solvents by the much lower solubility of the water, since on cooling a sealed tube containing water, alcohol, and the non-polar solvent, the opalescence accompanying the separation of the aqueous phase is very much fainter. Moreover, the irreproducibility of the values obtained with any one tube for the temperature at which the aqueous phase appeared could only be ascribed to variable supercooling effects. This was in marked contrast to the experiments with benzene, where the degree of reproducibility was very high, and where there was no reason to suppose that supercooling occurred to any significant extent.

As already explained, the variation with temperature of the solubility of water in any one alcohol–benzene solution obeys the relation $\log_{10} N = a - 10^3 b/T$. The factor b is, of course, proportional to the heat of solution, while the factor a is proportional to the entropy increase when a mole of water dissolves to give an arbitrary standard solution. In Fig. 4 values of a are plotted against b for all the mixtures of benzene with butanol, pentanol, and octanol which have been studied. The points conform to a straight line, except for those corresponding to the solutions of highest alcohol concentrations. In other words, at lower alcohol concentrations (but covering the range in which ΔH changes rapidly), there is a linear relation between the heat and entropy of solution of water. Other examples of this kind are known for binary solutions (see, *e.g.*, Butler, *Faraday Soc. Disc.*, Structure and Molecular Forces in Pure Liquids and Solutions, 1936, p. 229), but as yet they do not appear to have been given a satisfactory explanation.

We thank Mr. R. A. W. Hill for assisting with some of the measurements.

THE INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, April 26th*, 1951.]

560. *Syntheses in the Morphine Series. Part II.* Substituted Hexahydrodiphenyls and Related Topics.*

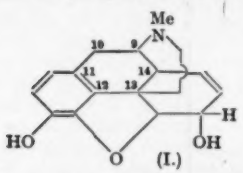
By J. A. Barltrop and J. S. Nicholson.

The Diels–Alder adducts derived from 2 : 3-dimethoxy-ω-nitrostyrene and butadiene or 2-ethoxybutadiene are transformed into 2-(2 : 3-dimethoxyphenyl)*cyclo*hexanone (VII) and 2-(2 : 3-dimethoxyphenyl)*cyclo*hexane-1 : 4-dione (XV) respectively. Preliminary experiments on the conversion of (VII) into substances more closely related to morphine are described.

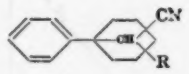
The reactions between arylmagnesium halides and α-cyano-α-*cyclo*hexylideneacetic ester and its derivatives are investigated.

This paper is largely concerned with the synthesis of intermediates containing a quaternary carbon atom substituted similarly to $C_{(13)}$ in morphine (I).

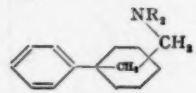
Birch and Robinson (*J.*, 1943, 502) discovered that aliphatic Grignard reagents react with ethyl α-cyano-α-*cyclo*hexylideneacetate by 1 : 4-addition, giving saturated compounds. Phenylmagnesium bromide has now been found to behave similarly, giving a 40% yield of ethyl α-cyano-α-1-phenyl*cyclo*hexylacetate (II; R = CO_2Et). The ester was hydrolysed with



(I.)

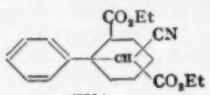


(II.)



(III.)

sodium carbonate solution to the corresponding acid (II; R = CO_2H), which was readily decarboxylated to 1-cyanomethyl-1-phenyl*cyclo*hexane (II; R = H). Reduction of the nitrile afforded the base (III; R = H), which was converted into the dimethylamino-compound (III; R = Me) by formaldehyde and formic acid. Since the completion of this work, the preparation of compounds similar to those described above has been reported; Brown, Cook, and Heilbron (*J.*, 1949, S 113) obtained a low yield of 2-2′-diethylaminoethyl-2-phenyl*cyclo*hexanone by alkylating 2-phenyl*cyclo*hexanone with 2-diethylaminoethyl chloride, and Boekelheide (*J. Amer. Chem. Soc.*, 1947, **69**, 790) alkylated 2-phenyl*cyclo*hexanone in the 2-position with chloropropionitrile.



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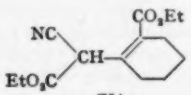

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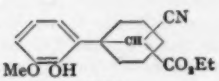


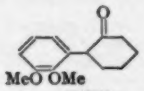
(VI.)

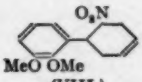
Attempts were made to extend the scope of the above synthesis to include molecules more closely related to morphine. First, in order to facilitate the construction of the phenanthrene 9 : 10-bridge, ethyl α-cyano-α-2-carbethoxy*cyclo*hexylideneacetate was condensed with phenylmagnesium bromide. The required product (IV) was, however, only obtained in very poor yield, presumably because the unsaturated ester tautomerised to (V). Secondly, in an attempt to introduce a more appropriately substituted benzene ring, the Grignard reagent derived from 3-iodoveratrole was added to α-cyano-α-*cyclo*hexylideneacetic ester, but there was obtained only a very small yield of a product believed to possess the structure (VI). The demethylation must have occurred during the actual preparation of the Grignard reagent, since carboxylation of the latter afforded guaiacolcarboxylic acid and not the expected 2 : 3-dimethoxybenzoic acid. A similar demethylation occurs when 2 : 3-dimethoxybenzonitrile reacts with methylmagnesium iodide (Amstutz, *J. Amer. Chem. Soc.*, 1949, **71**, 3836).

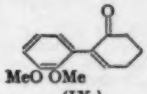
It has been realised for some time that 2-(2 : 3-dimethoxyphenyl)*cyclo*hexanone (VII) is potentially a useful intermediate for the synthesis of derivatives of morphine. It was first

* Part I, *J.*, 1947, 399.

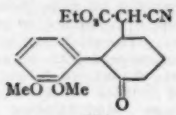
prepared by Horning, Horning, and Platt (*J. Amer. Chem. Soc.*, 1947, **69**, 2929) by a tedious synthesis, proceeding in 5% overall yield, from *o*-veratraldehyde, and more recently by Bergmann, Pappo, and Ginsburg (*J.*, 1950, 1369). We have devised a new and shorter synthesis which gives 20% overall yield.

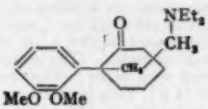

(VII.)

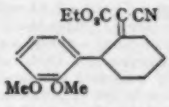

(VIII.)


(IX.)

2 : 3-Dimethoxy-ω-nitrostyrene, prepared by condensing *o*-veratraldehyde with nitromethane, when heated with butadiene at 200°, gave a 70% yield of 4-(2 : 3-dimethoxyphenyl)-5-nitro*cyclo*hexene (VIII), which was readily hydrogenated to the corresponding nitro*cyclo*hexane. By the reaction described first by Nef (*Annalen*, 1894, **280**, 263), 1-(2 : 3-dimethoxyphenyl)-2-nitro*cyclo*hexane was converted into its sodium salt and rapidly acidified. 2-(2 : 3-Dimethoxyphenyl)*cyclo*hexanone (VII) was thus obtained in 35% yield. The unsaturated nitro-compound (VIII) behaved similarly in the Nef reaction and gave 6-(2 : 3-dimethoxyphenyl)*cyclo*hex-3- or -2-enone; the position occupied by the double bond could not be determined with certainty from the ultra-violet absorption spectrum.

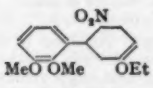

(X.)

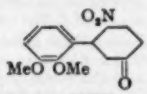

(XI.)

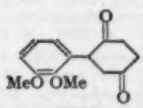

(XII.)

Bromination of (VII) gave 2-bromo-2-(2 : 3-dimethoxyphenyl)*cyclo*hexanone, which on dehydrobromination afforded the unsaturated ketone (IX), whence, by addition of cyanoacetic ester, we hoped to obtain the substance (X). The poor yields encountered in the preparation of (IX) (cf. Ginsburg and Pappo, *J.*, 1951, 516) prevented our accumulating sufficient material to investigate the Michael addition reaction. Nevertheless, a small quantity of a substance which may well possess the structure (X) was obtained by treating the bromodimethoxyphenyl-*cyclo*hexanone with sodiocyanoacetic ester.

The paper by Ginsburg and Pappo (*loc. cit.*) prompts us to report other attempts, as yet incomplete, to exploit the synthetical possibilities of dimethoxyphenyl*cyclo*hexanone. These have included alkylation with 2-diethylaminoethyl chloride to give 2-2′-diethylaminoethyl-2-(2 : 3-dimethoxyphenyl)*cyclo*hexanone (XI) and condensation with ethyl cyanoacetate. From the latter reaction the unsaturated ester (XII) was obtained in reasonable yield. Experiments on its conversion into a hydrophenanthrene are in progress.


(XIII.)

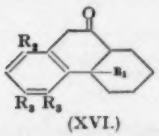

(XIV.)

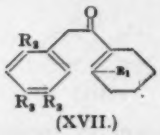

(XV.)

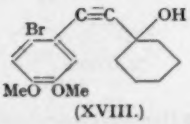
2-Ethoxybutadiene reacted smoothly with 2 : 3-dimethoxy-ω-nitrostyrene, giving 4-(2 : 3-dimethoxyphenyl)-2-ethoxy-5-nitro*cyclo*hexene (XIII). Theoretical considerations and Holmes and Mann's work (*J. Amer. Chem. Soc.*, 1947, **69**, 2000) make it certain that the product is the 2-ethoxy- rather than the 1-ethoxy-derivative. Hydrolysis with dilute acid afforded the nitro-ketone (XIV), from which, by the Nef reaction, 2-(2 : 3-dimethoxyphenyl)*cyclo*hexane-1 : 4-dione (XV) was obtained. This intermediate possesses a keto-group in a position equivalent to that of codeinone.

A different approach to the morphine system, which envisaged the preparation of systems of the type (XVI) by cyclising phenylacetyl*cyclo*hexenes (XVII), broke down because of the inaccessibility of these compounds. An attempted Darzens reaction between *cyclo*hexene and 2-bromo-4 : 5-dimethoxyphenylacetyl chloride was not successful. 2-Bromo-4 : 5-dimethoxyphenylacetylene, prepared by decarboxylation of the corresponding propiolic acid, proved to be most inert: it failed to react with sodium wire and, although it was converted into metallic

derivatives by treatment with ethylmagnesium bromide and with sodamide in liquid ammonia, these derivatives, on condensation with *cyclo*hexanone, gave only a 20% yield of 1-(2-bromo-4 : 5-dimethoxyphenylethynyl)*cyclo*hexanol (XVIII). This result agrees with findings by Fulton and Robinson (*J.*, 1933, 1463) who were unable to obtain any product from the Grignard


(XVI.)


(XVII.)


(XVIII.)

derivative of 3 : 4-dimethoxyphenylacetylene and *cyclo*hexene oxide. An attempt to isomerise the ethynylcarbinol (XVIII) to (XVII; $R_1 = H$, $R_2 = Br$, $R_3 = OMe$) (cf. Fischer and Löwenberg, *Annalen*, 1929, **475**, 183; Hurd and Christ, *J. Amer. Chem. Soc.*, 1937, **59**, 118) by boiling formic acid gave only black, intractable products. Sodiophenylacetylene and 2-ethyl-*cyclo*hexanone gave 2-ethyl-1-phenylethynyl*cyclo*hexanol, but this compound also could not be rearranged to an unsaturated ketone.

Experimental.

*Ethyl α-Cyano-α-1-phenyl*cyclo*hexylacetate*.—A solution of phenylmagnesium bromide [from bromobenzene (4·9 g.), magnesium (0·75 g.), and ether (20 c.c.)] was slowly added, with stirring, to an ice-cold solution of ethyl α-cyano-α-*cyclo*hexylideneacetate (5·5 g.) in ether (20 c.c.). The mixture was set aside for 20 minutes and then refluxed for 30 minutes. The complex was decomposed with ice and dilute sulphuric acid and the product isolated with ether. The residual oil was shaken for 1 hour with an aqueous solution of potassium cyanide (4 g.), then isolated with ether and distilled. *Ethyl α-cyano-α-1-phenyl*cyclo*hexylacetate* (3·3 g.) was collected at 160—170° (bath)/0·2 mm. Redistillation gave the ester as a viscous oil, b. p. 158—163° (bath)/0·2 mm. (Found : C, 74·9; H, 7·6. $C_{17}H_{21}O_2N$ requires C, 75·3; H, 7·7%).

*α-Cyano-α-1-phenyl*cyclo*hexylacetic Acid*.—The above ester (6·7 g.) was boiled for 6 hours with 10% sodium carbonate solution (150 c.c.). After being washed with ether, the aqueous solution was acidified and the liberated oil isolated with ether. It crystallised on trituration with chloroform–light petroleum. The *acid* was crystallised twice from chloroform–light petroleum (b. p. 60—80°), from which it separated in small clusters of needles, m. p. 123—124° (Found : C, 74·0; H, 6·9; N, 6·1. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·7%).

1-*Cyanomethyl*-1-*phenyl*cyclo*hexane*.—The above acid (4·2 g.) was decarboxylated by heating it to 200° (oil-bath). The *cyanide* (3·1 g.) was obtained as a colourless oil, b. p. 175—185° (bath)/9 mm. (Found : C, 84·5; H, 8·8; N, 7·0. $C_{14}H_{17}N$ requires C, 84·4; H, 8·5; N, 7·0%).

1-2′-*Aminoethyl*-1-*phenyl*cyclo*hexane*.—The above nitrile (2 g.), dissolved in boiling absolute ethanol, was treated with sodium (6·7 g.) added in small pieces during 15 minutes. The solution was acidified and steam-distilled. The residue was washed with ether and basified, and the liberated oil isolated with ether and distilled. The *amine* (1·6 g., 80%) was collected at 170—180° (bath)/9 mm. A portion of the base was converted into the *hydrochloride* by means of hydrogen chloride in ether. It separated from moderately concentrated hydrochloric acid in needles, m. p. 251—254° (Found : C, 69·6; H, 9·3; N, 5·9. $C_{14}H_{21}N,HCl$ requires C, 70·1; H, 9·2; N, 5·85%). The hydrochloride, on treatment with sodium picrate, afforded the *picrate*, which crystallised from 50% aqueous ethanol in plates, m. p. 178—180° (Found : C, 55·8; H, 5·6; N, 12·9. $C_{14}H_{21}N,C_6H_3O_7N_3$ requires C, 55·6; H, 5·6; N, 12·9%).

1-2′-*Dimethylaminoethyl*-1-*phenyl*cyclo*hexane*.—The above base (1·4 g.), dissolved in 90% formic acid (2·0 g.), was heated on the steam-bath for 6½ hours with 35% formaldehyde solution (1·8 c.c.). Hydrochloric acid (5 c.c.; 20%) was added and the whole evaporated to dryness under reduced pressure. The gummy hydrochloride was taken up in water, washed with ether, and basified, and the oil so obtained isolated with ether and distilled. The base (1 g.) was collected at 175—180° (bath)/9 mm. and converted into its *hydrochloride* with dry hydrogen chloride in ether. The salt separated from dry ethanol–ether in microscopic needles, m. p. 182—184° (Found : C, 71·7; H, 9·5; N, 4·8. $C_{16}H_{25}N,HCl$ requires C, 71·8; H, 9·7; N, 5·2%). The *picrate* crystallised from 90% ethanol in long blades, m. p. 169—171° (Found : C, 57·6; H, 6·0; N, 12·3. $C_{16}H_{25}N,C_6H_3O_7N_3$ requires C, 57·4; H, 6·1; N, 12·2%).

Ethyl α-(2-*Carbethoxy*-1-*phenyl*cyclo*hexyl*)-α-*cyanoacetate*.—A solution of phenylmagnesium bromide [from bromobenzene (2·64 g.), magnesium (0·4 g.), and ether (5 c.c.)] was added, with stirring, to a solution of ethyl α-2-carbethoxy*cyclo*hexylidene-α-cyanoacetate (4·0 g.) (Grewe and Mondon, *Ber.*, 1948, **81**, 279) in benzene (15 c.c.) at 0°. The mixture was refluxed for 4 hours, then decomposed with ice-cold dilute sulphuric acid, and the product isolated with ether. The oil so obtained was shaken with an excess of aqueous-alcoholic potassium cyanide to remove unchanged ester. The solution was then diluted with water and the product isolated with ether and distilled. The required *ester* (0·5 g.), a green viscous oil, was collected at 180—190° (bath/0·05 mm.) (Found : C, 69·5; H, 7·1. $C_{20}H_{25}O_4N$ requires C, 69·9; H, 7·3%).

*Ethyl α-Cyano-α-1-(2-hydroxy-3-methoxyphenyl)*cyclo*hexylacetate*.—A mixture of 2 : 3-dimethoxyiodobenzene (1·1 g.) (Mauthner, *J. pr. Chem.*, 1937, **149**, 328), activated magnesium (0·2 g.), ether (0·3 c.c.), and anisole (2·5 c.c.) was heated to 130°. After 2—3 hours the reaction started and the

Grignard complex separated on the sides of the flask and on the magnesium. After a further hour's heating the mixture was cooled, stirred, treated with ethyl α-cyano-α-*cyclo*hexylideneacetate (1·2 g.) in benzene (10 c.c.), and boiled until homogeneous (1 hour). The complex was decomposed and submitted to treatment with potassium cyanide as above. Distillation of the product gave two fractions: (1) a colourless liquid, b. p. 135—140° (bath)/0·05 mm. (Found: C, 67·7; H, 8·2%), and (2) the *ester*, a gum, b. p. 240—250° (bath)/0·05 mm. (Found: C, 68·2; H, 7·2. $C_{18}H_{23}O_4N$ requires C, 68·2; H, 7·2%).

2-*Hydroxy*-3-*methoxybenzoic Acid*.—2 : 3-Dimethoxyiodobenzene (0·5 g.) was converted into the Grignard derivative as described above and treated with solid carbon dioxide. The complex was decomposed with ice and dilute sulphuric acid and extracted with ether, and the ethereal solution extracted with sodium carbonate solution. Acidification of the extract gave guaiacolcarboxylic acid (40 mg.), m. p. and mixed m. p. 142—146°.

2 : 3-*Dimethoxy*-ω-*nitrostyrene*.—2 : 3-Dimethoxybenzaldehyde (33·2 g.) in ethanol (250 c.c.) and nitromethane (12·3 g.) was cooled in ice and treated with a solution of sodium hydroxide (8·2 g.) in water (10 c.c.), slowly and with stirring. After 30 minutes, the mixture was poured into an excess of 17% hydrochloric acid. The precipitated *nitro-styrene* was collected and crystallised from ethanol. It formed massive yellow needles (32 g., 77%), m. p. 86° (Found: C, 57·2; H, 5·1; N, 6·3. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%).

4-(2 : 3-*Dimethoxyphenyl*)-5-*nitro*cyclo*hexene*.—The above nitro-styrene (10·4 g.) and butadiene (12 c.c.), dissolved in pure dry xylene, were heated in a sealed tube at 200° for 14 hours. Evaporation of the solvent left a black mass, which separated from ethanol in crystals (9·2 g., 70%), m. p. 80—82°. The *adduct* crystallised from light petroleum (b. p. 60—80°) in long colourless rods, m. p. 81—83° (Found: C, 64·0; H, 6·3; N, 5·2. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%).

1-(2 : 3-*Dimethoxyphenyl*)-2-*nitro*cyclo*hexane*.—The above nitro-compound (0·5 g.) in acetic acid (5 c.c.) was hydrogenated over platinum oxide (20 mg.). The theoretical quantity of hydrogen was rapidly absorbed. The solution, filtered from catalyst, on dilution with water gave 1-(2 : 3-*dimethoxyphenyl*)-2-*nitro*cyclo*hexane* (0·45 g.), which separated from light petroleum (b. p. 60—80°) in colourless blades, m. p. 81—82·5° (Found: C, 63·5; H, 7·5; N, 5·6. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2; N, 5·3%).

2-(2 : 3-*Dimethoxyphenyl*)cyclo*hexylamine*.—1-(2 : 3-Dimethoxyphenyl)-2-nitro*cyclo*hexane (0·25 g.) in ethanol (4 c.c.) was hydrogenated over Raney nickel at 50°/1 atm. After uptake of the theoretical amount of hydrogen, the filtrate from catalyst was evaporated under reduced pressure. The residue was taken up in dry ether and the *hydrochloride* of 2-(2 : 3-*dimethoxyphenyl*)cyclo*hexylamine* (0·2 g.) was precipitated with hydrogen chloride. The substance separated from ethanol–ether in needles, m. p. 228—230° (Found: C, 62·2; H, 8·3; N, 5·3. $C_{14}H_{21}O_2N$,HCl requires C, 61·9; H, 8·1; N, 5·2%).

6-(2 : 3-*Dimethoxyphenyl*)-3- or -2-cyclo*hexenone*.—4-(2 : 3-Dimethoxyphenyl)-5-nitro*cyclo*hexene (0·5 g.) was transformed into its sodium salt with an excess of ethanolic sodium hydroxide and added dropwise to 2N-sulphuric acid (50 c.c.) maintained at 0°. A small quantity of crystalline *ketone* separated overnight. It was collected and crystallised from ethanol and then from light petroleum (b. p. 60—80°) as colourless prisms (50 mg.), m. p. 96—98° (Found: C, 72·5; H, 7·2. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%), $\lambda_{max.}$ 2200 and 2700 A., $\varepsilon_{max.}$ = 9040 and 1600 respectively (in methanol).

2-(2 : 3-*Dimethoxyphenyl*)cyclo*hexanone*.—Sodium hydroxide (5 g.) in ethanol (20 c.c.) was added to a solution of 1-(2 : 3-dimethoxyphenyl)-2-nitro*cyclo*hexane (4·8 g.) in ethanol (30 c.c.), and the whole added slowly, with agitation, to 10% sulphuric acid (400 c.c.) cooled to 0°. After being kept in ice for 15 minutes, the mixture was warmed to 60°, then cooled, and the product isolated with ether and distilled. The ketone (2·4 g.), b. p. 180—190° (bath)/0·1 mm., separated from ether–light petroleum in crystals, m. p. 67—69° (Found: C, 71·6; H, 7·9. Calc. for $C_{14}H_{18}O_3$: C, 71·8; H, 7·7%). Horning and Platt (*loc. cit.*) give m. p. 67—69°. The *semicarbazone* separated from ethanol in prisms, m. p. 193—194° (decomp.) (Found: C, 62·4; H, 7·4; N, 14·9. $C_{15}H_{21}O_3N_3$ requires C, 61·9; H, 7·2; N, 14·4%). After regeneration from the semicarbazone, the ketone had m. p. 70—71°. Bergmann, Pappo, and Ginsburg (*loc. cit.*) record m. p. 70—71°.

2-*Bromo*-2-(2 : 3-*dimethoxyphenyl*)cyclo*hexanone*.—A solution of the dimethoxyphenyl*cyclo*hexanone (0·5 g.) in acetic acid (5 c.c.) was cooled, treated dropwise with bromine (0·35 g.) in acetic acid (5 c.c.), and the whole was poured into water. The precipitated *bromo-ketone* (0·5 g.) was collected and dried. It crystallised from ethanol or ethyl acetate–light petroleum in stout prisms, m. p. 112—113° (decomp.) (Found: C, 53·2; H, 5·8. $C_{14}H_{17}O_3Br$ requires C, 53·7; H, 5·5%).

2-(2 : 3-*Dimethoxyphenyl*)cyclo*hex*-2-*enone*.—The above bromo-ketone (0·2 g.) was boiled for 30 minutes with pyridine (5 c.c.), then poured into dilute sulphuric acid and extracted with ether. The residue from the ethereal extract was taken up in ether and light petroleum (b. p. 60—80°) and on evaporation, gave the unsaturated ketone (15 mg.). It separated from light petroleum (b. p. 60—80°) in prisms, m. p. 85—86·5° (Found: C, 71·7; H, 7·0. Calc. for $C_{14}H_{16}O_3$: C, 72·4; H, 6·8%). Ginsburg and Pappo (*loc. cit.*) give m. p. 96°.

Condensation between 2-*Bromo*-2-(2 : 3-*dimethoxyphenyl*)cyclo*hexanone and Ethyl Sodiocyanoacetate*.—Ethyl cyanoacetate (0·7 g.) was converted into its sodium derivative in benzene (20 c.c.) and boiled under reflux for 6 hours with the bromo-ketone (1·0 g.). After being acidified and washed with water, the benzene layer was evaporated and the residue boiled for 4 hours with 10% sodium carbonate solution (50 c.c.). The non-acidic material was isolated with ether and distilled. A colourless oil was collected at 180—190° (bath)/0·02 mm. The *ketone* crystallised from light petroleum (b. p. 80—100°) in colourless blades, m. p. 112—113° (Found: C, 66·9; H, 7·0. $C_{19}H_{23}O_3N$ requires C, 66·1; H, 6·7%).

Ethyl α-Cyano-α-2-(2 : 3-dimethoxyphenyl)cyclohexylideneacetate.—2-(2 : 3-Dimethoxyphenyl)*cyclo*hexanone (0·7 g.) was boiled under reflux with ethyl cyanoacetate (0·3 g.), acetic acid (0·4 c.c.), ammonium acetate (0·2 g.), and benzene (5 c.c.) for 7 hours at 160° (oil-bath) and the water formed was continuously separated. The mixture was diluted with ether, washed with concentrated sodium carbonate solution and with water, and distilled. *Ethyl α-cyano-α-2-(2 : 3-dimethoxyphenyl)cyclohexylideneacetate* (0·5 g.), a colourless oil, was collected at 190—195° (bath)/0·01 mm. (Found : C, 68·9; H, 7·3; N, 4·6. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·0; N, 4·25%).

2-2′-Diethylaminoethyl-2-(2 : 3-dimethoxyphenyl)cyclohexanone.—Dimethoxyphenyl*cyclo*hexanone (0·7 g.) in toluene (10 c.c.) was added to a solution of sodamide, prepared by dissolving sodium (0·1 g.) in liquid ammonia (10 c.c.), and the mixture was set aside for 2 hours to allow the ammonia to evaporate. The mixture was stirred and treated with 2-diethylaminoethyl chloride (0·7 g.) in toluene (10 c.c.). The temperature was raised to 85° during 1 hour and kept at that point for 5 hours with stirring. After the mixture had been finally boiled for 1 hour, the bases were extracted with dilute hydrochloric acid. The aqueous extract was washed with ether, then basified, and the liberated bases were isolated with ether and distilled. Two fractionations gave the *amino-ketone* as an oil (0·3 g.), b. p. 185—195° (bath)/0·01 mm. (Found : N, 4·35. $C_{22}H_{31}O_3N$ requires N, 4·25%). The base gave no crystalline derivatives except an extremely hygroscopic methiodide.

2-Ethoxy-4-(2 : 3-dimethoxyphenyl)-5-nitrocyclohexene.—2 : 3-Dimethoxy-ω-nitrostyrene (2 g.) in dry xylene (5 c.c.) was heated at 200° for 15 hours with 2-ethoxybutadiene (1·3 g.) (Holmes and Mann, *J. Amer. Chem. Soc.*, 1947, **69**, 2000) and quinol (30 mg.). Distillation afforded a viscous, yellow oil, b. p. 190—210° (bath)/0·1 mm., which on redistillation gave the enol *ether* (2·3 g.), b. p. 195—205° (bath)/0·1 mm. (Found : C, 63·0; H, 6·9; N, 4·9. $C_{18}H_{25}O_5N$ requires C, 62·5; H, 6·8; N, 4·6%). The substance could not be hydrogenated over platinum oxide at 40° and atmospheric pressure.

3-(2 : 3-Dimethoxyphenyl)-4-nitrocyclohexanone.—A solution of the above ether (0·5 g.) in methanol (50 c.c.) was kept for 1·5 hours with 6N-sulphuric acid (2 c.c.) and water (3 c.c.). The mixture was copiously diluted with water, and the *ketone* isolated with ether. The gum so obtained crystallised when warmed with ether. Recrystallisation from ether gave long, colourless prisms (0·3 g.), m. p. 94·5—96·5° (Found : C, 60·1; H, 6·1; N, 4·4. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1; N, 5·0%). In alcoholic solution, the ketone gave an amorphous *2 : 4-dinitrophenylhydrazone*, which became crystalline in boiling benzene. Crystallisation from acetic acid and then from xylene gave orange-yellow prisms, m. p. 212° (decomp.) (Found : C, 52·5; H, 4·7. $C_{20}H_{21}O_8N_5$ requires C, 52·3; H, 4·6%).

2-(2 : 3-Dimethoxyphenyl)cyclohexane-1 : 4-dione.—The above nitro-ketone (0·4 g.), dissolved in ethanol (5 c.c.), was treated with sodium hydroxide (0·5 g.) in ethanol, and the resulting yellow solution added dropwise to ice-cold 2N-sulphuric acid (50 c.c.). After a short time, the solution was warmed to 60°, then cooled, and the dark solution extracted with ether. Distillation of the dried ethereal extract gave a colourless oil, b. p. 185—195° (bath)/0·06 mm., which crystallised on trituration with ether. The *diketone* (60 mg.) separated from ether in stout prisms, m. p. 96—98° (Found : C, 67·4; H, 6·5. $C_{14}H_{14}O_4$ requires C, 67·8; H, 6·5%).

2-Bromo-4 : 5-dimethoxyphenylpropiolic Acid.—(*A*) Ethyl 3 : 4-dimethoxycinnamate (30 g.) in chloroform (150 c.c.) was slowly treated with bromine (40·7 g.) in chloroform (50 c.c.) and left overnight. Evaporation of the chloroform under reduced pressure gave a gum, which was boiled under reflux for 7 hours with a solution of potassium hydroxide (35 g.) in ethanol (300 c.c.). The ethanol was distilled, water was added, and the solution filtered. On acidification, a brown oil separated, which crystallised on storage. Three recrystallisations from aqueous methanol gave the *propiolic acid* as colourless plates, m. p. 178° (decomp.) (Found : C, 43·9; H, 3·6. $C_{11}H_9O_4Br,H_2O$ requires C, 43·6; H, 3·6%).

(*B*) Ethyl 2-bromo-4 : 5-dimethoxycinnamate (19·6 g.) was converted into the dibromide as above and refluxed with a solution of potassium hydroxide (27·3 g.) in ethanol (150 c.c.) for 7 hours. Similar working up gave the propiolic acid (11 g.), m. p. 178° (decomp.) alone or when mixed with the specimen prepared as above.

2-Bromo-4 : 5-dimethoxyphenylacetylene.—The above propiolic acid (4 g.) in diethylaniline (15 c.c.) was kept at 180° until evolution of carbon dioxide ceased (*ca.* 30 minutes). The mixture was poured into dilute sulphuric acid, and the precipitated solid taken up in ether and washed with dilute sulphuric acid, sodium carbonate solution, and water. Distillation of the ether gave a brown solid, which when steam-distilled afforded *2-bromo-4 : 5-dimethoxyphenylacetylene* (2·4 g.) in the distillate. The compound crystallised from light petroleum (b. p. 80—100°) in rhombs, m. p. 101—102° (Found : C, 50·2; H, 3·7. $C_{10}H_9O_2Br$ requires C, 49·8; H, 3·7%).

1-(2-Bromo-4 : 5-dimethoxyphenylethynyl)cyclohexanol.—The above acetylene (1·2 g.) in ether (15 c.c.) was added to a solution of ethylmagnesium bromide [from ethyl bromide (0·8 g.), magnesium (0·12 g.), and ether (3 c.c.)]. A brown solid separated. The whole was refluxed for 30 minutes and treated with *cyclo*hexanone (5 g.) in benzene (10 c.c.). After being boiled for 1 hour and kept overnight, the solution was decomposed with ammonium chloride solution and extracted with ether. Steam-distillation of the residue from the ethereal extract gave unchanged acetylene (0·4 g.) in the distillate. The residual non-volatile material was isolated with ether, dissolved in chloroform–light petroleum (4 : 1), and passed down an alumina column. The eluted *alcohol* (0·2 g.) crystallised from light petroleum (b. p. 80—100°) in fine needles, m. p. 116—117° (Found : C, 56·9; H, 5·4. $C_{16}H_{19}O_3Br$ requires C, 56·6; H, 5·6%). The same yield of product was obtained by performing the condensation in the presence of sodamide in liquid ammonia.

*Attempted Preparation of 2-Bromo-4 : 5-dimethoxyphenyl cyclo*Hex*-1-enyl Ketone.*—(*A*) The above alcohol (0·2 g.) was refluxed for 45 minutes with 90% formic acid (2 c.c.). The black solution was poured into dilute sodium hydroxide solution and extracted with ether. Evaporation of the ether left an intractable gum, which would form no satisfactory ketonic derivatives.

(*B*) Stannic chloride (1·7 g.) was added to a solution of 2-bromo-4 : 5-dimethoxyphenylacetyl chloride (1·9 g.) in carbon disulphide (30 c.c.), cooled to −10°, and treated slowly with a solution of *cyclo*hexene (0·55 g.) in carbon disulphide (10 c.c.). Next morning, the carbon disulphide was decanted and the residual black mass treated with ice-cold hydrochloric acid and ether. The ethereal extract was washed with dilute hydrochloric acid, sodium carbonate, and water, dried, and evaporated. The residual oil was boiled for 2 hours with diethylaniline and poured into dilute hydrochloric acid. Ether-extraction yielded a gummy material which resisted all methods of purification, including chromatography.

2-*Ethyl*-1-*phenylethynyl*cyclo*hexanol*.—Phenylacetylene (2 g.) was converted into its sodium salt with sodium wire (0·46 g.) in ether (10 c.c.). 2-Ethyl*cyclo*hexanone (2·5 g.) (King, Barltrop, and Walley, *J.*, 1945, 277) in ether (10 c.c.) was slowly added to the suspension of the sodium salt and the whole refluxed for one hour. The homogeneous solution was treated with dilute hydrochloric acid and extracted with ether. The ether yielded an oil which was steam-distilled to remove starting materials. The residue was isolated with ether and distilled. 2-*Ethyl*-1-*phenylethynyl*cyclo*hexanol* (2·1 g.) was collected at 200—205° (bath)/13 mm. as a colourless oil, n_D^{25} 1·5585 (Found : C, 84·3; H, 9·1. $C_{16}H_{20}O$ requires C, 84·2; H, 8·8%).

Attempted Preparation of Benzyl 2-*Ethyl*cyclo*hex*-1-*enyl Ketone*.—The above ethynyl alcohol (0·5 g.) was boiled for 30 minutes with 90% formic acid (10 c.c.), and poured into dilute sodium hydroxide solution, and extracted with ether. Distillation of the ether gave an oil which contained some ketonic material, but no pure substance could be isolated.

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 19th*, 1951].

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561. *Some Derivatives of* N-*Phenacylaniline.*

By D. L. PAIN and R. SLACK.

The action of formaldehyde on *N*-acyl derivatives of some *N*-*p*-nitrophenacylanilines has been examined. *N*-Chloroacetyl-*N*-phenacylanilines react with bases to give intramolecular dehydrohalogenated products, probably by way of an intermediate enol. *N*-*p*-Nitrophenacylaniline reacts readily with ethyl chloroformate and with nitrous fumes.

LONG and TROUTMAN (*J. Amer. Chem. Soc.*, 1949, **71**, 2473) have described the hydroxymethylation of α-acetamido-*p*-nitroacetophenone to give (±)-2-acetamido-1-*p*-nitrophenylpropane-1 : 3-diol, an intermediate of value in the synthesis of chloramphenicol [(+)-*threo*-2-dichloroacetamido-1-*p*-nitrophenylpropane-1 : 3-diol]. It seemed possible that aryl analogues (*e.g.*, I; R = CO·$CHCl_2$, R′ = aryl) of the antibiotic might be obtained by application of a

(I.) *p*-NO_2·C_6H_4·CH(OH)·CH(NRR′)·CH_2·OH *p*-NO_2·C_6H_4·CO·CH_2·NRR′ (II.)

similar sequence of reactions to *N*-phenacylanilines (II; R = acyl, R′ = aryl). Moreover, dearylation of this type of compound (*e.g.*, I; R = H, R′ = *p*-NO·C_6H_4) by alkaline hydrolysis would give the intermediate 2-amino-1-*p*-nitrophenylpropane-1 : 3-diol useful in the synthesis of chloramphenicol.

However, a study of the reactivity towards formaldehyde of the methylene group in compounds of type (II; R = acyl, R′ = aryl) suggested that hydroxymethylation might well be uncontrollable. Using potassium carbonate as catalyst, Long and Troutman (*ibid.*, p. 2469) found that α-benzamidoacetophenone and formaldehyde gave 2 : 4-dibenzamido-1 : 5-diphenylpentane-1 : 5-dione but that α-acetamido-*p*-nitroacetophenone (*ibid.*, p. 2463) (II; R = H, R′ = Ac), formaldehyde, and sodium hydrogen carbonate gave the required hydroxymethyl compound (I; R = H, R′ = Ac). We believed that the single alteration from R = H to R = Ph in (II) would increase the electron mobility—and hence the reactivity—about the methylene group to such an extent that substituted methanes, rather than hydroxymethyl compounds, would invariably be formed. Experiment has shown that this is so and, although a wide variety of conditions have been examined, we have been quite unable to stop these reactions at the hydroxymethyl stage.

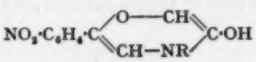
p-Nitrophenacyl bromide reacted readily with anilines and substituted anilines, except those bearing a bulky electro-negative substituent in the *ortho*-position. Thus *N*-*p*-nitro-

phenacyl derivatives of aniline and *o*- and *m*-chloroaniline were easily prepared, but anthranilic acid reacted sluggishly. Reaction with *o*-nitroaniline was too slow to be of practical value.

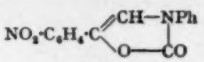
N-p-Nitrophenacylaniline, with the appropriate acid chlorides or anhydrides, gave acetyl, chloroacetyl, dichloroacetyl, and benzoyl derivatives; *o*- and *m*-chloro-*N-p*-nitrophenacylaniline gave the corresponding acetyl compounds.

Attempts to effect monohydroxymethylation of these amides are described in the Experimental section. From reactions with aqueous formaldehyde or paraformaldehyde and a basic catalyst 2 : 4-bisacetarylamido-1 : 5-di-*p*-nitrophenylpentane-1 : 5-diones, $CH_2[CH(NAcAr)\cdot CO\cdot C_6H_4\cdot NO_2]_2$, were obtained in which Ar was phenyl, *o*- or *m*-chlorophenyl.

Attempted hydroxymethylations of chloroacetylated aniline derivatives provided anomalous results of interest. No reaction occurred with formaldehyde in the presence of organic bases, sodium hydrogen carbonate, or potassium carbonate. With sodium hydroxide, however, the elements of hydrogen chloride were readily eliminated and *N-p*-nitrophenacyl-*N*-chloroacet-anilide and -*m*-chloroanilide gave, respectively, crystalline products which are



(III.)



(IV.)

considered to be probably the 1 : 4-oxazines (III; R = Ph and *m*-Cl·C_6H_4 respectively). Intervention of the enol–hydroxy-group of phenacylanilines in ring formation has been observed by McCombie and Parkes (*J.*, 1912, 1991). McCombie and Scarborough (*J.*, 1913, 56) were unable to condense *N*-phenacylaniline itself with ethyl chloroformate but obtained 3 : 5-diphenyloxazol-2-one by the direct action of carbonyl chloride. *N-p*-Nitrophenacylaniline, however, reacted with ethyl chloroformate in pyridine to give 5-*p*-nitrophenyl-3-phenyloxazol-2-one (IV). The possibility of ring-closure involving one or other of the benzene nuclei has been carefully considered in all these cases, but the experimental conditions employed seem to preclude this. The extreme reactivity in the enol forms naturally cast doubts on the structure of the compounds derived by reaction of the various phenacylanilides with formaldehyde. Spectral evidence, however, did not indicate *O*-alkylation in the condensation products.

N-p-Nitrophenacylaniline reacted quantitatively with nitrous fumes (cf. Möhlau *Ber.*, 1882, 15, 2472) to give the corresponding *N*-nitroso-compound (II; R = NO) but attempts either to condense this with formaldehyde or to effect migration of the nitroso-group into the *para*-position led to the regeneration of *N-p*-nitrophenacylaniline. Although the loss of a *N*-nitroso-group is fairly common, extreme lability towards both acid and alkali, as was here the case, is less usual.

Experimental.

N-p-*Nitrophenacylaniline.*—*p*-Nitrophenacyl bromide (9 g.) in alcohol (75 c.c.) was shaken at room temperature with aniline (8·5 g.) for 3 hours. The N-p-*nitrophenacylaniline* was filtered off, washed with alcohol, and recrystallised from benzene in dark-red needles (7·8 g.), m. p. 146° (Found: C, 64·9; H, 4·5; N, 10·9. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7; N, 10·9%).

o-*Chloro*-N-p-*nitrophenacylaniline.*—*p*-Nitrophenacyl bromide (16 g.) in hot alcohol (130 c.c.) was treated with *o*-chloroaniline (17 g.) and refluxing continued for 15 minutes. o-*Chloro*-N-p-*nitrophenacylaniline* (6·5 g.) was collected and recrystallised from alcohol in orange needles, m. p. 166—168° (Found: N, 9·65; Cl, 11·9. $C_{14}H_{11}O_3N_2Cl$ requires N, 9·6; Cl, 12·2%). Further heating of the liquors gave a crop of less pure material (13 g.).

The m-*chloro*-isomer, prepared similarly, formed orange needles (8·5 g.), m. p. 163—164°, from methanol (Found: N, 9·6%).

N-p-*Nitrophenacylanthranilic Acid.*—This *acid*, obtained from the bromide (4·9 g.) and anthranilic acid (2·8 g.) in alcohol (20 c.c.), formed microcrystalline red prisms (from nitrobenzene), m. p. >300° (Found: N, 9·1. $C_{15}H_{12}O_5N_2$ requires N, 9·3%).

N-p-*Nitrophenacylacetanilide.*—*N-p*-Nitrophenacylaniline (1·0 g.) was heated at 100° for 10 minutes with acetic anhydride (5 c.c.), and the mixture then poured on ice. The *amide* (100% yield) crystallised from methanol, giving colourless plates, m. p. 117—118° (Found: C, 64·7; H, 4·9; N, 9·4. $C_{16}H_{14}O_4N_2$ requires C, 64·4; H, 4·7; N, 9·4%).

The o-*chloroanilide*, prepared similarly (1 hour), formed plates, m. p. 131°, from methanol (Found: N, 8·4. $C_{14}H_{11}O_4N_2Cl$ requires N, 8·4%). The p-*chloro*-isomer formed, from aqueous acetic acid, pale yellow prisms, m. p. 156—157° (Found: N, 8·35%).

N-p-*Nitrophenacylchloroacetanilide*, m. p. 155—156° (Found: N, 8·45; Cl, 10·0. $C_{16}H_{13}O_4N_2Cl$ requires N, 8·4; Cl, 10·7%), was prepared from *N-p*-nitrophenacylaniline (2·6 g.) and chloroacetyl chloride (6 g.) at 100° (5 minutes). Similarly was obtained N-p-*nitrophenacylchloroaceto*-m-*chloroanilide*, needles (from benzene–light petroleum), m. p. 156—157° (Found: N, 7·5; Cl, 19·6. $C_{16}H_{12}O_4N_2Cl_2$ requires N, 7·65; Cl, 19·35%).

N-p-*Nitrophenacylbenzanilide*, obtained from *N-p*-nitrophenacylaniline (2·6 g.) and benzoyl chloride (10 c.c.) at 100° (15 minutes), formed prisms (from methanol), m. p. 193—194° (Found: N, 7·4. $C_{21}H_{16}O_4N_2$ requires N, 7·3%).

Reactions with Formaldehyde.—The general procedure in all cases was to dissolve or suspend the amide in methanol, alcohol, or dioxan containing a trace of catalyst and to add the appropriate quantity (usually 1·0—1·5 mols.) of aqueous formaldehyde (40%) or paraformaldehyde with stirring. After varying periods, reaction mixtures were poured into water containing a little acetic acid, and the products collected and examined.

N-p-Nitrophenacylacetanilide was recovered unchanged after many experiments, but the conditions tabulated led to 2 : 4-*bisacetanilido*-1 : 5-*di*-p-*nitrophenylpentane*-1 : 5-*dione* in 30—70% yield (optimum with potassium carbonate). It crystallised in pale yellow prisms, m. p. 146°, from alcohol or ethyl acetate (Found: C, 65·1; H, 4·6; N, 9·2. $C_{33}H_{28}O_6N_4$ requires C, 65·1; H, 4·85; N, 9·2%).

Catalyst.	Solvent.	Temp.	Time.	Catalyst.	Solvent.	Temp.	Time.
$NaHCO_3$	EtOH	50—60°	2½ days	K_2CO_3 †	MeOH	50°	½ hr.
,,	,,	50	2½ hr.*	,,	EtOH	50	½ hr.
,,	,,	100	½ hr.	,,	,,	35	3 hr.
NaOH	Dioxan	18	12 hr.*				

* Reaction incomplete. † Paraformaldehyde used.

2 : 4-*Bisacet*-o-*chloroanilido*-, m. p. 133—135° (prisms from methanol) (Found: N, 8·15. $C_{33}H_{29}O_6N_4Cl_3$ requires N, 8·3%). 2 : 4-*bisacet*-m-*chloroanilido*-, m. p. 154—155° (prisms from ethyl acetate) (Found: N, 8·3; Cl, 10·5. $C_{33}H_{28}O_6N_4Cl_2$ requires N, 8·3; Cl, 10·5%), and 2 : 4-*bisbenzanilido*-1 : 5-*di*-p-*nitrophenylpentane*-1 : 5-*dione*, m. p. 156° (prisms from methanol) (Found: C, 70·5; H, 4·4; N, 7·5. $C_{43}H_{32}O_6N_4$ requires C, 70·5; H, 4·4; N, 7·6%), were similarly prepared. Dioxan containing traces of sodium hydroxide was the most satisfactory reaction medium in these cases.

Action of Sodium Hydroxide on N-p-*Nitrophenacylchloroacetanilide.*—The amide (0·3 g.) and 2 drops of aqueous sodinm hydroxide solution (35%) in alcohol (5 c.c.) were heated at 50° for 1 hour. The solid was collected and recrystallised from alcohol to give yellow needles, m. p. 182—183°. The same product (3-*hydroxy*-6-p-*nitrophenyl*-4-*phenyl*-1 : 4-*oxazine*) was obtained, whether or not formaldehyde was added to the reaction mixture (Found: C, 64·0; H, 4·1; N, 9·5. $C_{15}H_{12}O_4N_2$ requires C, 64·8; H, 4·05; N, 9·45%).

Action of Triethylamine on N-p-*Nitrophenacylchloroaceto*-m-*chloroanilide.*—The amide (0·37 g.) and anhydrous triethylamine (3 drops) in alcohol (2 c.c.) were heated at 50° for 3 hours. The clear solution was diluted with water and the resulting solid, after recrystallisation from alcohol, gave 3-*hydroxy*-4-m-*chlorophenyl*-6-p-*nitrophenyl*-1 : 4-*oxazine* as yellow needles, m. p. 174° (Found: N, 8·1; Cl, 10·6. $C_{16}H_{11}O_4N_2Cl$ requires N, 8·35; Cl, 10·75%). The same product was obtained when aqueous sodium hydroxide replaced triethylamine. Formaldehyde did not affect the course of the reaction.

Action of Ethyl Chloroformate on N-p-*Nitrophenacylaniline.*—*N-p*-Nitrophenacylaniline (2·6 g.) and ethyl chloroformate (1·1 g.) in dry pyridine (30 c.c.) were heated at 100° for 30 minutes and the solution was then poured into water. The resulting gum was extracted with chloroform and the extract washed with dilute sulphuric acid, water, and aqueous sodium hydrogen carbonate. The solution was dried ($MgSO_4$) and evaporated *in vacuo*, the residue being recrystallised from benzene–light petroleum (b. p. 80—100°), to give 5-p-*nitrophenyl*-3-*phenyloxazol*-2-*one* as yellow needles, m. p. 223—225° (Found: C, 63·4; H, 4·0. $C_{15}H_{10}O_4N_2$ requires C, 63·8; H, 3·6%).

N-p-*Nitro*-N-*nitrosophenacylaniline.*—The *sec.*-amine (2·6 g.) was suspended in alcohol at 0° and nitrous fumes (from arsenic trioxide and nitric acid) were passed into the mixture until the red colour disappeared. The pale yellow solid (100%) was collected and recrystallised from benzene to give colourless plates of the N-*nitroso*-compound, m. p. (decomp.) 138—139° (Found: C, 59·4; H, 4·0; N, 15·0. $C_{15}H_{11}O_4N_3$ requires C, 58·9; H, 3·9; N, 14·7%). *N-p*-Nitrophenacylaniline was rapidly regenerated by the action of acid or base.

The authors thank Dr. A. J. Ewins, F.R.S., for his interest, Mr. S. Bance, B.Sc., for semi-microanalyses, and the Directors of May & Baker Ltd. for permission to publish these results.

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Dagenham, Essex.

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562. *The Nature of the Co-ordinate Link. Part III.* Improved Preparation of Tertiary Phosphine, Arsine, and Stibine Complex Compounds with Platinous Chloride.*

By J. Chatt and R. G. Wilkins.

Jensen's method for the preparation of the isomeric $(R_3M)_2PtCl_2$ (M = P, As, or Sb) yields a mixture of isomers. Often one isomer is present only in very small quantity. A method is devised for converting the crude product, almost quantitatively, into either isomer, except in the two limiting cases, (1) when spontaneous isomerisation is rapid and only the less soluble *cis*-isomer can be isolated, and (2) when the equilibrium between the two isomers is so far on the *trans*-side that only the *trans*-isomer can be isolated.

The complex compounds formed by tertiary phosphines, arsines, and stibines with platinous chloride are readily prepared by shaking a suspension of the organic ligand in aqueous potassium chloroplatinite (Jensen, *Z. anorg. Chem.*, 1936, **229**, 237). The products from the tertiary alkyl phosphines and arsines are usually mixtures of *cis*- and *trans*-$(R_3M)_2PtCl_2$ (M = P or As). The stibines have invariably given only *cis*-$(R_3Sb)_2PtCl_2$. The isomers are easily separated by extraction of the *trans*-isomer with ether or light petroleum (b. p. 40—60°), leaving the *cis*-isomer as a completely insoluble residue. The only serious difficulty occurs if the required isomer is formed in very small quantity, which is frequently the case. Thus Jensen was unable to obtain any *cis*-bis(tri-*n*-propylarsine)dichloroplatinum, and in numerous preparations of bis(tri-*n*-propylphosphine)dichloroplatinum we rarely obtained more than 10% of the *trans*-isomer, but on one occasion obtained 20%. The preparation by the reaction of the phosphine on the bridged complex, $(Pr_3P)_2Pt_2Cl_4$, has also given very variable ratios with as much as 85% of the *trans*-isomer (Chatt, *J.*, 1950, 2306).

A study of the equilibrium *cis*- $\rightleftharpoons$ *trans*-$(Pr_3M)_2PtCl_2$ (where M = P, As, or Sb) has led us to devise means of producing almost entirely the required isomer, except in the stibine series where only the *cis*-isomer can be obtained crystalline. Our observations apply particularly to the tri-*n*-propyl series but are of wider validity if we make allowance for the reduced solubility and shift of the above equilibrium to the left in lower homologues, to the right when the chlorine is replaced by more covalently bound acid radicals, *e.g.*, bromine, iodine, or nitrito, and to the left by less covalently bound radicals, *e.g.*, nitrate. A limitation of our method is imposed by spontaneous isomerisation of some isomers. This occurs particularly when the platinum atom is combined with atoms from the higher series of the Periodic Table, *e.g.*, iodine, tellurium, or antimony. Thus we were unable to obtain from solution the very soluble *trans*-$(Pr_3Sb)_2PtCl_2$ although the less soluble *cis*-isomer is well known.

The conversion of the crude product from Jensen's preparation into the required isomer depends on the following observations: (1) The equilibrium between stable isomers in solution can be labilised by the addition of a trace of the free ligand. Thus approx. 0·002 g. of tri-*n*-propylphosphine added to 50 c.c. of a benzene solution of 1 g. of either isomeric $(Pr_3P)_2PtCl_2$ causes equilibrium to be established in 15 minutes at 25°. (2) The catalysed lability can be frozen and the spontaneous isomerisation can be arrested, sometimes completely for a short time as in the arsenic series, by addition of a trace of the corresponding bridged complex (Chatt, *J.*, 1951, 652) sufficient to remove all the free ligand, *e.g.*, $2Pr_3P + (Pr_3P)_2Pt_2Cl_4 = 2(Pr_3P)_2PtCl_2$. (3) The equilibrium lies well to the side of the *trans*-isomer, *e.g.*, there is 97% of *trans*-$(Pr_3P)_2PtCl_2$, 99·8% of the arsine, and 80% of the stibine analogue in the equilibrium mixture with the corresponding *cis*-isomers in benzene solution at 25°. (4) The *cis*- are considerably less soluble in all solvents than the *trans*-isomers, and particularly they are almost insoluble in ether and light petroleum which dissolve the *trans*-isomers readily. (5) The effect of spontaneous isomerisation can be greatly reduced by rapid recrystallisations and immediate drying of the crystalline product at 0·01 mm.

When the *trans*-isomer is required, the mixed isomers, as prepared (Jensen, *loc. cit.*), are dissolved in benzene, the equilibrium established by addition of a trace of the free ligand, then frozen by addition of bridged complex. The *trans*-isomer, together with its small equilibrium concentration of *cis*-isomer, is obtained by evaporation of the solution and can then be extracted entirely from the *cis*-isomer by light petroleum or another suitable solvent.

* Part II, *J.*, 1951, 652.

The *cis*-isomer is obtained by evaporating the labilised equilibrium solution, preferably in light petroleum; the less soluble *cis*-isomer, in spite of its low concentration relative to the *trans*-isomer, separates, and as evaporation proceeds all the *trans*- is converted into the *cis*-isomer from which the catalyst may be washed with light petroleum.

Difficulty is experienced when there is so little *cis*-compound in the equilibrium that the *trans*-compound separates on evaporation of the labilised equilibrium mixture, and also when the tendency to spontaneous isomerisation is so great that isomerisation cannot be arrested sufficiently by addition of the bridged compound. The preparation of the tri-*n*-propyl series of complexes supplies examples of all possible combinations of circumstances, except those when only the *trans*-isomer can be isolated. In such an event, the *cis*-isomer may be obtained indirectly provided that spontaneous isomerisation can be prevented, as Jensen (*loc. cit.*, p. 239) obtained *cis*-$(Pr_3P)_2PtI_2$ by the reactions: *cis*-$(Pr_3P)_2PtCl_2 + Ag_2SO_4 \longrightarrow$ *cis*-$(Pr_3P)_2Pt(SO_4) + 2KI \longrightarrow$ *cis*-$(Pr_3P)_2PtI_2$.

Experimental.

The light petroleum used in these preparations had b.p. 40—60°. All the *cis*-isomers described here are completely insoluble in light petroleum. The complete solubility of a sample of *trans*-isomer provided a quick and reliable test that it contained no *cis*-isomer.

cis-*Bis*(*tri*-n-*propylphosphine*)*dichloroplatinum*.—Crude $(Pr_3P)_2PtCl_2$ (3·6 g.) obtained by reaction of tri-*n*-propylphosphine with aqueous potassium chloroplatinite (Jensen, *loc. cit.*) was suspended in warm light petroleum (30 c.c.). About 0·005 g. of tri-*n*-propylphosphine in 1 c.c. of light petroleum was added and equilibrium established within a few minutes. The solution was then evaporated to dryness at 15—20 mm. and entirely *cis*-material separated (3·6 g.). This was washed with light petroleum, then twice recrystallised from ethanol (yield, 2·0 g. plus 0·8 g. from the mother-liquors). It had m. p. 150·5—152° (Jensen gives m. p. 149—150°).

trans-*Bis*(*tri*-n-*propylphosphine*)*dichloroplatinum*.—Crude $(Pr_3P)_2PtCl_2$ (1·5 g.) was dissolved in benzene (20 c.c.), and tri-*n*-propylphosphine (about 0·002 g.) added. After 30 minutes dichlorobis(tri-*n*-propylphosphine)-$\mu\mu'$-dichlorodiplatinum (0·006 g.) was added. The solution was evaporated at 15—20 mm. and the dry residue extracted with light petroleum, leaving a small white residue of the *cis*-isomer. The yellow extract was evaporated to dryness and the residue twice recrystallised from ethanol, yielding pure *trans*-isomer (0·7 g., plus 0·45 g. from the mother-liquors), m. p. 85—86° (Jensen gives m. p. 82—82·5°).

cis-*Bis*(*tri*-n-*propylarsine*)*dichloroplatinum*.—The direct reaction of tri-*n*-propylarsine with aqueous potassium chloroplatinite (as in Jensen's preparation) gave us only the *trans*-isomer. Crude $(Pr_3As)_2PtCl_2$ (4·6 g.) in warm light petroleum (20 c.c.) was isomerised by tri-*n*-propylarsine (0·006 g.). The solution was evaporated to dryness at 15—20 mm. and the solid residue treated with light petroleum (*ca.* 20 c.c.) and re-evaporated. This treatment was repeated until the residue consisted entirely of the crude *cis*-material. This was washed with light petroleum several times to remove any trace of catalyst and recrystallised twice from methanol, yielding pure cis-*isomer* (2·2 g., plus 1·7 g. from the mother-liquors), m. p. 131—132·5° (Found: C, 32·15; H, 6·2. $C_{18}H_{42}Cl_2As_2Pt$ requires C, 32·1; H, 6·3%).

trans-*Bis*(*tri*-n-*propylarsine*)*dichloroplatinum*.—This is most readily obtained by recrystallisation of crude $(Pr_3As)_2PtCl_2$ from methanol but can be obtained from the *cis*-isomer. The *cis*-isomer (4·5 g.) in warm benzene (25 c.c.) was isomerised with tri-*n*-propylarsine (0·003 g.) (15 minutes). Dichloro(tri-*n*-propylarsine)-$\mu\mu'$-dichlorodiplatinum (0·008 g.) was added and the solution evaporated to dryness. The residue, consisting almost entirely of the *trans*-compound, was recrystallised several times from methanol (until completely free from the *cis*-isomer). Pure *trans*-isomer (4·0 g.) was obtained, having m. p. 52—53° (Jensen gives m. p. 51—52°).

The above arsine complexes, to be sufficiently pure not to isomerise slowly but spontaneously in benzene solution, must be dried immediately under *ca.* 0·01 mm. pressure.

cis-*Bis*(*tri*-n-*propylstibine*)*dichloroplatinum*.—This was prepared by direct reaction between tri-*n*-propylstibine and aqueous potassium chloroplatinite. Recrystallised several times from ethanol it had m. p. 79—80° (Jensen gives m. p. 80—81°). The product, even after careful drying at 0·01 mm., isomerised slowly in pure benzene, equilibrium being reached in about 2 days. Drying in a vacuum-desiccator in the normal manner gave a product which isomerised much more quickly, equilibrium being reached in 1½—2 hours.

Attempted Preparation of trans-*Bis*(*tri*-n-*propylstibine*)*dichloroplatinum*.—Addition of dichlorobis-(tri-*n*-propylstibine)-$\mu\mu'$-dichlorodiplatinum (*ca.* 0·008 g.) to an equilibrium mixture of $(Pr_3Sb)_2PtCl_2$ (1·5 g.) in benzene which contained about 80% of *trans*-isomer, followed by evaporation of the solution at 15—20 mm., gave a dark-red oil which did not crystallise but isomerised rapidly to the solid canary-yellow *cis*-compound.

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563. *The* Euphorbia *Resins. Part VI.* The Oxidative Degradation of the Side Chain of Euphol and Tirucallol.*

By R. N. E. Bennett, Hs. K. Krusi, and F. L. Warren.

The oxidation of euphadienyl acetate with potassium permanganate gives acetoxydiketotrisnoreuphenic acid (II), $C_{29}H_{42}O_6$, which is hydrolysed to the hydroxy-acid (III), $C_{27}H_{40}O_5$, identical with eupholic acid obtained directly by a similar oxidation by Dupont, Dulou, and Vilkas (*Bull. Soc. chim.*, 1949, **16**, 811). The two forms of the methyl ester of (III) reported by Dupont *et al.* are found to be the methyl esters of (II) and (III).

Oxidation of euphadienyl acetate with chromic acid proceeds similarly, to give (III) which is identical with the acid previously formulated by Krusi (*J.*, 1950, 2864) as $C_{25}H_{36}O_5$.

The " noreupholic acid " of Vilkas, Dupont, and Dulou (*Bull. Soc. chim.*, 1949, **16**, 813) is shown to be dehydroeupholic acid (triketotrisnoreuphenic acid), $C_{27}H_{36}O_5$.

The evidence for the existence of a hexenyl chain in euphol is accordingly not established.

Oxidation of tirucalladienyl acetate with potassium permanganate gives compounds isomeric with those obtained similarly from euphadienyl acetate.

The reducible ethylenic linkage in euphol (euphadienol), $C_{30}H_{50}O$, was shown by McDonald, Warren, and Williams (*J.*, 1949, S155) to exist as an *iso*propylidene grouping forming part of a longer chain. Krusi (*J.*, 1950, 2864) reported that the action of *N*-bromosuccinimide on euphadienyl acetate gave an " acetate mixture " containing euphatrienyl acetate in which the additional double bond was thought to be conjugated with the original *iso*propylidene group. Furthermore the oxidation of the " acetate mixture " with chromic acid was stated to yield an acetoxy-diketo-acid, isolated as its methyl ester (II'), $C_{28}H_{40}O_6$, m. p. 170—171°. This ester was hydrolysed to a hydroxy-diketo-acid (III'), $C_{25}H_{36}O_5$, m. p. 233—234°, which with diazomethane gave a methyl ester (IV'), $C_{26}H_{38}O_5$, m. p. 185—186°.

Dupont, Dulou, and Vilkas (*Bull. Soc. chim.*, 1949, **16**, 811) had previously oxidised euphadienyl acetate with potassium permanganate to eupholic acid, $C_{27}H_{40}O_5$, m. p. 231—231·5°, which with methyl sulphate gave a mixture of two forms of a methyl ester, m. p. 160·5—161° and m. p. 190—190·5°, from which methyl eupholate, $C_{28}H_{42}O_5$, m. p. 184° was isolated. The similarity in melting point of eupholic acid and Krusi's hydroxy-diketo-acid (III'), as well as of their methyl esters, seemed significant in that the French workers indicated the possibility of a C_{26}-formula, whilst Krusi's analytical figures did not exclude the formulation of his C_{25} acid as a C_{26} acid. On the other hand Vilkas, Dupont, and Dulou (*ibid.*, p. 813) reported that oxidation of euphone, as well as of eupholic acid, with chromic acid gave " noreupholic acid," $C_{26}H_{38}O_5$. Before applying similar oxidations to isomeric triterpenes from the *Euphorbia* species these degradations were re-investigated.

Oxidation of euphadienyl acetate with potassium permanganate under the conditions described by Dupont *et al.* (*loc. cit.*) gave a semi-solid acid from which a yellow acid, m. p. 230—230·5°, was obtained as reported by these workers. Recrystallisation from aqueous alcohol gave light yellow needles having the same melting point and analysing after being dried in a high vacuum, to the same formula, although the French workers reported the isolation of a colourless crystalline monohydrate, m. p. 245·5—246·5°. The oily residue from the mother-liquors was readily converted by boiling alcoholic potash into the same solid acid which was thus obtained in a larger yield. The methyl ester, prepared by the action of diazomethane, was carefully chromatographed over alumina to show the homogeneity of the compound. Our analytical figures, particularly those of the acid obtained by way of the methyl ester or after hydrolysis of the oxidation product, confirmed the C_{27} formulation of the hydroxy-acid. Thus the oxidation of euphadienyl acetate (I*b*) with potassium permanganate gives acetoxy-diketotrisnoreuphenic acid (V) which is partly hydrolysed during the process to hydroxy-diketotrisnoreuphenic (eupholic) acid (III), $C_{27}H_{40}O_5$, m. p. 231—232°, yielding a methyl ester

* Part V, *J.*, 1951, 2864.

(IV), $C_{28}H_{42}O_5$, m. p. 188—188·5°. The second form of the methyl ester, m. p. 160·5—161°, reported but not analysed by Dupont *et al.* (*loc. cit.*), is almost certainly the methyl ester of the unhydrolysed acetoxy-acid (V). The oxidation of euphadienyl acetate with potassium permanganate in neutral solution and esterification of the product gave the methyl ester (II), $C_{30}H_{44}O_6$, m. p. 163—164°. The ester (II) and its hydrolysis product (III), m. p. 229—231°, showed no depression of their melting points when mixed with compounds (II′) and (III′) above respectively.

$C_{30}H_{46}$ { —CH·CH:CMe$_2$; —CH$_2$·C:C·CH$_2$· ; >CH·OR

(*Ia*; R = H.)
(*Ib*; R = Ac.)

$C_{29}H_{44}$ { —CH·CO$_2$R′ ; —CO·C:C·CO· ; >CH·OR

(II; R = Ac, R′ = Me.)
(III; R = H, R′ = H.)
(IV; R = H, R′ = Me.)
(V; R = Ac, R′ = H.)

$C_{30}H_{44}$ { —CH·CO$_2$R′ ; —CO·C:C·CO· ; >CO

(VI; R′ = H.)
(VII; R′ = Me.)

These experiments indicated that the acid (III′) was identical with (III) for which the C_{27} formula seems now established. The compound (III′), obtained in over 50% yield (Krusi, *loc. cit.*), was almost certainly the oxidation product of euphadienyl acetate and not of euphatrienyl acetate, which, according to the value given for the extinction coefficient, probably comprises much less than 50% of the "acetate mixture." To confirm this, euphadienyl acetate was oxidised with chromic acid under exactly the same conditions as described for the oxidation of the "acetate mixture." There resulted an acetoxy-diketo-acid, m. p. 146—147°, giving a methyl ester, m. p. 168—169°, which was hydrolysed to an acid, m. p. 230—232°. The melting point of this acetoxy-diketo-acid methyl ester and of its hydrolysis product showed no depression when these compounds were mixed with (II′) and (III′) above respectively. The low values for carbon, approximating to the C_{25} formula, cannot be accounted for by hydration as the hydrate is unstable under the conditions of drying, and they remain unexplained.

Direct oxidation of euphadienol with chromium trioxide gave an acid which was esterified to methyl triketotrisnoreuphenate (VII), $C_{28}H_{40}O_5$, m. p. 142—143°, whilst Vilkas *et al.* (*loc. cit.*) give for methyl noreupholate, m. p. 140·5—141·5°. The supposed "noreupholic acid" (see above) is really dehydroeupholic acid (VI) formed from eupholic acid (III) by oxidation of the secondary hydroxyl group.

The C_{27} formulations given above were further confirmed by the oxidation of tirucallyl (tirucalladienyl) acetate (*Ib*) which Haines and Warren (*J.*, 1949, 2554; 1950, 1562) showed was isomeric with euphadienyl acetate. Oxidation with potassium permanganate and complete hydrolysis of the product gave hydroxydiketotrisnortirucallenic acid (III), $C_{27}H_{40}O_5$, m. p. 211—212°, yielding a methyl ester (IV), $C_{28}H_{42}O_5$, m. p. 183—184°. The extinction curves of these oxidation products show a maximum similar to that found for the corresponding compounds from euphol, and the chromophoric group is certainly ·CO·C:C·CO·. The above tirucallenic acid (III) and its methyl ester (IV) showed pronounced depression of their melting points when they were mixed with the isomeric eupholic acid (III) and methyl eupholate (IV) respectively.

Vilkas *et al.* (*loc. cit.*) and Krusi (*loc. cit.*) had deduced by different reasoning that the side chain of euphol contained the grouping –CH$_2$·CH$_2$·CH:CMe$_2$. The experimental evidence, however, as now represented only permits the conclusion that a five-carbon chain is present as in (I). The ease of hydrolysis of methyl eupholate (IV) as well as of methyl dehydroeupholate (VII) (cf. Vilkas *et al.*, *loc. cit.*) necessitates that the carboxyl group is not tertiary. The parallel experiments with tirucalladienol (*Ia*) establish the existence of a similar side chain.

Experimental.

Microanalyses are by Weiler and Strauss, Oxford. All m. p.s are uncorrected. Light absorptions were determined in alcohol.

Oxidation of Euphadienyl Acetate with Alkaline Potassium Permanganate.—Euphadienyl acetate (10 g.) was added to a solution of potassium permanganate (20 g.) in acetone (2 l.), and the whole stirred for 24 hours. The excess of permanganate was destroyed with sulphur dioxide, the solution filtered, and the manganese mud extracted (Soxhlet) with methanol. The combined methanol and acetone solutions were evaporated under reduced pressure, the residue was poured into water, and the solution, acidified with hydrochloric acid, was extracted with ether. The ethereal extract was shaken with sodium carbonate solution, and the acid precipitated from the carbonate extract with hydrochloric acid and re-extracted with ether. This ethereal extract gave a yellow-orange oil (6 g.) which, lixiviated with ether, left a solid which crystallised from ethanol in yellow rhombohedra, m. p. 230—230·5°

(Found: C, 73·4; H, 9·1%; equiv., 431·3, 441·6). The m. p. of this acid was not depressed when it was mixed with the hydroxy-diketo-acid obtained by the oxidation of euphadienyl acetate with chromic acid (see below). Crystallisation from aqueous ethanol (1 : 1) gave the acid as light yellow needles, m. p. 231—232° (Found: C, 73·4; H, 9·1%). The combined oily and solid crude acid product was hydrolysed with 5% alcoholic potassium hydroxide and then all the acid was obtained as a solid which, crystallised from ethanol, gave hydroxydiketotrisnoreuphenic (eupholic) acid as rhombohedra, m. p. 231—232°, showing $\lambda_{max.}$ 272·5 mμ. (log ε 3·93) (Found: C, 72·85; H, 8·85%; equiv., 454, 455. Calc. for $C_{27}H_{40}O_5$: C, 72·9; H, 9·1%; equiv., 444·6). The crude hydrolysed acid oxidation product was treated with diazomethane in ether, and the resulting neutral ester (4 g.) in light petroleum–benzene (5 : 1) was chromatographed through alumina (100 g.; activity I—II), and the column developed with light petroleum–benzene (1 : 1). No apparent separation occurred and the solid product, crystallised three times from methanol, gave methyl hydroxydiketotrisnoreuphenate (eupholate) as fine greenish-yellow needles, m. p. 186°, $[\alpha]_D^{20}$ +18·7° in chloroform (c = 1), showing $\lambda_{max.}$ 272·5 mμ. (log ε 3·95) (Found: C, 72·8, 73·05; H, 9·0, 8·9. Calc. for $C_{28}H_{42}O_5$: C, 73·3; H, 9·2%). The methyl ester sublimed at 170° in a high vacuum, giving stout yellow needles, m. p. 188—188·5° (Found: C, 73·2; H, 9·4%). Hydrolysis of the methyl ester with 10% alcoholic potassium hydroxide and two crystallisations of the product from absolute ethanol gave the acid as light greenish-yellow rhombohedra, m. p. 230—231° (Found: C, 72·7, 73·1; H, 9·1, 9·2%; equiv., 439, 442).

Oxidation of Tirucalladienyl Acetate with Potassium Permanganate.—Tirucalladienyl acetate (3 g.) was oxidised with potassium permanganate (6 g.) in acetone (900 ml.) as above, and the acid product hydrolysed by boiling alcoholic potassium hydroxide. The hydroxy-acid was isolated as a yellow solid which was difficult to crystallise and was esterified with diazomethane. An ethereal solution of the product was shaken with sodium carbonate solution to remove unesterified acid, and the solvent removed. The crystalline solid, dissolved in light petroleum–benzene (2 : 1), was filtered through alumina (20 g.; activity I—II). Two crystallisations from methanol gave *methyl hydroxydiketotrisnortirucallenate*, m. p. 183—184°, showing $\lambda_{max.}$ 272·5 mμ. (log ε 3·95) (Found: C, 73·1, 73·2; H, 8·9, 9·1. $C_{28}H_{42}O_5$ requires C, 73·3; H, 9·2%). Hydrolysis of the methyl ester with alcoholic potassium hydroxide and crystallisation of the product from methanol gave the *acid* as light greenish-yellow needles, m. p. 211—212°, $\lambda_{max.}$ 272·5 mμ. (log ε 3·94) (Found: C, 72·9, 72·9; H, 9·05, 8·9; equiv., 445, 435. $C_{27}H_{40}O_5$ requires C, 72·9; H, 9·1%; equiv., 444·6). The acid left unesterified in the formation of the methyl ester crystallised from aqueous ethanol in matted yellow needles, m. p. 190—198°, and from methanol in yellow needles, m. p. 212—213°, showing $\lambda_{max.}$ 272·5 mμ. (log ε 3·94) (Found: C, 72·6, 72·7; H, 9·0, 9·0%; equiv., 441, 445).

Oxidation of Euphadienyl Acetate with Potassium Permanganate in Neutral Solution.—Euphadienyl acetate (2·1 g.) in acetone (200 ml.) was stirred with aluminium sulphate (3 g.) whilst potassium permanganate (4·2 g.) in acetone (100 ml.) was added at room temperature, and the mixture was then refluxed for 4 hours. The excess of permanganate was destroyed with formaldehyde, and the acid product, isolated as described above, was treated with diazomethane. The neutral ester was chromatographed over alumina and crystallised from methanol, to give a methyl acetoxy-diketo-ester, m. p. 163—164° after sintering at 160°, undepressed on being mixed with the compound, m. p. 168—169° (see below) from the chromic acid oxidation (Found: C, 71·7; H, 8·5. Calc. for $C_{33}H_{44}O_8$: C, 71·9; H, 8·9. Calc. for $C_{33}H_{42}O_8$: C, 71·6; H, 8·7%). Hydrolysis with alcoholic potassium hydroxide and crystallisation of the product from acetone–water gave the hydroxy-diketo-acid, m. p. 229—231° after sintering at 225°, which showed no depression when the compound was mixed with the hydroxy-diketo-acid (see below) obtained from the oxidation of euphadienyl acetate with chromic acid.

Oxidation of Euphadienyl Acetate with Chromium Trioxide.—Euphadienyl acetate was oxidised and the product worked up as described previously for the "acetate mixture" by Krusi (*loc. cit.*). The potassium hydrogen carbonate extract gave an acid which, crystallised from acetone–water, yielded an *acetoxy-diketo-acid*, m. p. 146—147°, which was dried at 100° in a high vacuum for analysis (Found: C, 69·8; H, 8·9. $C_{29}H_{42}O_6$ requires C, 71·6; H, 8·7. $C_{27}H_{38}O_6$ requires C, 70·7; H, 8·35%). This acid gave the methyl acetoxy-diketo-ester, m. p. 168—169°, and the hydroxy-diketo-acid, m. p. 230—232° (Found, after drying at 100° in a high vacuum: C, 72·2; H, 8·95. Calc. for $C_{27}H_{40}O_5$: C, 72·9; H, 9·1. Calc. for $C_{28}H_{38}O_5$: C, 72·15; H, 8·7%). This methyl ester and its hydrolysis product showed no depression of their melting points when mixed with compounds (II′) and III′) from the "acetate mixture" respectively.

Oxidation of Euphol with Chromium Trioxide.—Euphol (1·3 g.) was treated with chromic acid and the product worked up as above. The methyl ester in light petroleum–benzene (10 : 1; 50 ml.) was filtered through alumina (12 g.), and the column developed with the same mixture (5 : 1; 70 ml.). The product was crystallised from methanol, to give *methyl triketotrisnoreuphenate*, m. p. 142—143°, sintering at 138°, which was sublimed at 140° in a high vacuum for analysis (Found: C, 73·6; H, 8·8. $C_{28}H_{40}O_5$ requires C, 73·6; H, 8·8%).

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564. *The* Euphorbia *Resins. Part VII.* The Characterisation of the Groups in Euphorbol.*

By J. B. Barbour, F. L. Warren, and D. A. Wood.

The latices from *E. triangularis* and *E. ingens* contain euphol and euphorbol, and from *E. triangularis* also tirucallol.

Euphorbadienyl (euphorbyl) acetate was oxidised to yield the following substances: (i) Ozonolysis gave formaldehyde. (ii) Osmic acid and hydrolysis yielded euphorbenetriol which was oxidised further to ketonor-euphorbenol. (iii) Perbenzoic acid formed α- and β-epoxyeuphorbenyl acetate.

Euphorbenyl acetate with chromic acid gave diketoeuphorbenyl acetate containing the group ·CO·C:C·CO·.

Thus euphorbadienol contains a secondary hydroxyl group, an active ethylenic linkage as a methylene group, and an inactive ditertiary double bond between two methylene groups.

Continuing our studies of the resins from the *Euphorbia* species we have reinvestigated the latices from *E. triangularis* and *E. ingens* from which euphol was previously reported by McDonald, Warren, and Williams (*loc. cit.*). The latex from *E. ingens* is a powerful vesicant when left on the skin, and the dust from the crude resin causes painful swelling of the face and reddening of the eyes. The splashing of small drops into the eye during the tapping of the trees causes acute pain from which relief is only given by washing with borax.

Chromatographic separation of the resins and acetylation of the several fractions gave from the petroleum fraction euphyl acetate, and from the benzene fraction a mixture, m. p. 89—92°, which yielded euphorbyl acetate only after numerous crystallisations. The resin from *E. triangularis* gave also a small quantity of tirucallyl acetate, m. p. 159—160°, which had previously only been obtained from *E. tirucalli* (cf. Haines and Warren, *J.*, 1949, 2554; 1950, 1562).

Euphorbol, first isolated by Bauer and Schenkel (*Arch. Pharm.*, 1928, **266**, 633), was characterised by Newbold and Spring (*J.*, 1944, 249) as a tetracyclic triterpene alcohol having one reducible and one non-reducible ethylenic bond. Our euphorbol was identified by the preparation of its acetate as well as of dihydroeuphorbol and dihydroeuphorbyl acetate the properties of which corresponded with those reported by Newbold and Spring (*loc. cit.*). Euphorbyl acetate was obtained in about 5—7% yield according to the season of collection of both species; but purification from *E. triangularis* proved more difficult owing to the presence of tirucallyl acetate, and the two corresponding alcohols were not readily separable by chromatographic methods. The mixture of the two acetates appeared as plates, m. p. 118—120°, and the isolation of euphorbyl acetate as needles, m. p. 124—125°, was a tedious process. These difficulties were not encountered when using the resin from *E. ingens*.

The oxidation of euphorbadienol (euphorbol) and euphorbenol gave respectively euphorbadienone and euphorbenone, which showed no strong absorption in the near ultra-violet and were characterised further as their oximes. These ketones differ from the corresponding ketones from euphol (cf. Bennett and Warren, *J.*, 1950, 697) and from tirucallol (Haines and Warren, 1950, *loc. cit.*).

Ozonolysis of euphorbadienyl acetate was reported by Bauer and Schenkel (*loc. cit.*) as giving formic acid. In view of the isolation of formaldehyde from the ozonolysis of the *iso*-propylidene group in euphadienyl acetate (cf. McDonald, Warren, and Williams, *J.*, 1949, S 155), this experiment was repeated. Formaldehyde, identified as its dimedone compound, m. p. 189°, was found and no trace of acetone was detected, so that the active ethylenic linkage is present as a methylene group. No other product could be isolated pure from the ozonolysis; but the crude product showed no reactions for methyl ketones.

The treatment of euphorbadienyl acetate with osmic acid and hydrolysis of the product gave in small yield euphorbenetriol, m. p. 191—192°, but falling to m. p. 173—174° after sublimation. This triol was oxidised with lead tetra-acetate to ketonoreuphorbenol. With a view to obtaining larger quantities of the glycol, euphorbadienyl acetate was oxidised with one

* Part VI, preceding paper.

molecular proportion of perbenzoic acid whereupon two products, α- and β-epoxyeuphorbenyl acetates, m. p. 157° and 143° respectively, were readily obtained.

The inactive double bond is seemingly situated as in euphadienol and tirucalladienol (Haines and Warren, *loc. cit.*). Chromic acid oxidation of euphorbenyl acetate readily gave diketoeuphorbenyl acetate, which was hydrolysed to diketoeuphorbenol, which in turn was oxidised to diketoeuphorbenone. These compounds showed a maximum absorption at 272·5 mμ. (log $\varepsilon_{max.}$ 3·94) in alcohol, which is indicative of the grouping ·CO·C:C·CO·.

Euphorbadienol is thus a tetracyclic triterpene secondary alcohol containing one methylene group joined directly to a ring and one ethylenic linkage situated between two methylene groups, ·CH_2·C:C·CH_2·. It thus differs from the two isomeric compounds euphadienol and tirucalladienol, which occur associated with it in the plant, in that the active ethylenic linkage is present as a methylene and not an *iso*propylidene group.

Experimental.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.

Extraction.—The trees located in the Umgeni Valley, Natal, were tapped in the early morning when the flow of sap is fastest. The fresh latex was poured in a thin stream into boiling alcohol, and the solid material extracted with successive lots of hot alcohol. The alcoholic solution, concentrated under reduced pressure, deposited on cooling an amorphous solid.

(*a*) The solid (300 g.) from *E. triangularis* Desf. was dissolved in benzene, and the solvent removed completely under reduced pressure. The residual brown solid was dissolved in light petroleum (b. p. 50—70°) and chromatographed through alumina (1250 g.; activity I—II). Light petroleum (25 l.) eluted a colourless solid (200 g.), m. p. *ca.* 106—112°; benzene (19 l.) eluted a yellow waxy solid (52·5 g.); and ether removed brown gums (12 g.).

The petroleum fraction gave on acetylation euphadienyl acetate (2·5 g.), m. p. 108—109°, leaving a colourless crystalline solid (180 g.), m. p. 90—95°, unchanged on further crystallisation. The benzene fraction was acetylated and the product crystallised from ethanol and finally from acetone, to give euphorbyl (euphorbadienyl) acetate (7 g.), m. p. 124—125°, hydrolysed to euphorbadienol, m. p. 126—127°, and hydrogenated to euphorbenyl acetate, m. p. 133—134°, which gave euphorbenol, m. p. 132—133°. Newbold and Spring (*J.*, 1944, 255) give m. p.s 124—125°, 126—127°, 133—135°, and 132·5—134·5° respectively for these compounds. The mother-liquors from the crystallisation of euphorbyl acetate slowly deposited a white amorphous solid, m. p. 89—92°, and hard white nodules, m. p. 130—134°. On warming of the solution the amorphous solid dissolved, and the white nodules, which were filtered off, crystallised from acetone to yield tirucallyl acetate (1·2 g.), m. p. 159—160°, undepressed on admixture with an authentic specimen.

(*b*) The resin (50 g.; m. p. 110—112°) from *E. ingens* in light petroleum (600 ml.; b. p. 50—70°) was filtered through deactivated alumina and then chromatographed on a column of alumina (500 g.; 6·5 × 36 cm.) activated at 300°. Elution with six 5-l. portions of light petroleum (b. p. 50—70°) yielded 11·1, 4·8, 3·5, 2·4, 2·1, and 1·3 g. respectively, and subsequent elution with four 5-l. portions of light petroleum (b. p. 60—90°) yielded 1·9, 1·6, 1·4, 1·8 g. respectively. The above fractions were acetylated and the acetates recrystallised several times from ethanol, to give euphadienyl acetate, m. p. 108° (Found: C, 81·6; H, 11·1. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). The mother-liquors gave euphorbadienyl acetate, m. p. 124—125° (Found: C, 82·0; H, 11·3. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%), further characterised as euphorbenyl acetate, m. p. 134° (Found: C, 81·5; H, 11·6. Calc. for $C_{32}H_{54}O_2$: C, 81·6; H, 11·6%). Further elution of the column with benzene (5 l.) gave a solid (9·4 g.) which on acetylation and recrystallisation of the product from ethanol gave euphorbadienyl acetate, m. p. 124—125°. Continued elution with benzene (10 l.) and then with ether (5 l.) gave intractable oils.

Euphorbadienone.—Euphorbadienyl acetate (1·1 g.) was hydrolysed with alcoholic potassium hydroxide, the dried euphorbadienol (0·9 g.) heated to 250° in an atmosphere of carbon dioxide, copper oxide powder added, the temperature raised to 300°, and the whole heated for a further 10 minutes. The product in light petroleum (b. p. 50—70°) was filtered through alumina (10 g.) to give a white solid which, crystallised from ethanol, gave *euphorbadienone* as rectangular plates, m. p. 95°, $[\alpha]_D^{17}$ +22° (*c* = 1 in chloroform) (Found: C, 84·7; H, 11·8. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). The *oxime* crystallised from ethanol as plates, m. p. 238—239° (Found: C, 81·8; H, 11·3; N, 3·2. $C_{30}H_{49}ON$ requires C, 81·9; H, 11·2; N, 3·2%).

Euphorbenone.—Euphorbenol (800 mg.) in benzene (36 ml.) was stirred for 36 hours at room temperature with chromium trioxide (1·2 g.) in water (12 ml.) and acetic acid (36 ml.). Methanol (2 ml.) was added, and the lower layer was separated from the benzene solution and extracted three times with benzene. The combined benzene solutions were washed with water and aqueous sodium hydrogen carbonate. Evaporation of the solvent gave a yellow oil (600 mg.) which was dissolved in light petroleum (b. p. 50—70°) and chromatographed through alumina (15 g.; grade I—II). The first petroleum eluate (120 ml.) gave a light yellow oil (530 mg.) which solidified readily in an evacuated desiccator to an amorphous solid, m. p. 88°. Three crystallisations from ethanol gave *euphorbenone* (130 mg.) as colourless flat needles, m. p. 96—97°, $[\alpha]_D^{20}$ +3·9° in chloroform (*c*, 0·7), $\lambda_{max.}$ 295 mμ., log ε 1·36 in hexane (Found: C, 84·05; H, 11·9. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). The *oxime* crystallised from ethanol in plates, m. p. 244—245° (Found: C, 82·1; H, 11·7; N, 3·0. $C_{30}H_{51}ON$ requires C, 81·7; H, 11·6; N, 3·2%).

Ozonolysis of Euphorbadienyl Acetate.—Euphorbadienyl acetate (600 mg.) in pure chloroform was ozonised for 4 hours and the chloroform removed under reduced pressure. The yellow solid was heated gently under reflux with water (70 ml.) for 30 minutes, and 10 ml. were distilled off. The distillate gave with dimedone colourless needles, m. p. 189°, undepressed when mixed with the formaldehyde compound. The remainder (9 ml.) of the distillate was treated with potassium permanganate and redistilled. This second distillate showed no tests for acetone.

Euphorbenetriol.—Euphorbadienyl acetate (1·82 g.) and osmic acid (0·98 g.) in dry ether (75 ml.) gave immediately a black solution which was set aside for 6 days. The ether was removed under reduced pressure, and the product refluxed with benzene (70 ml.), ethanol (70 ml.), potassium hydroxide (3·5 g.), and mannitol (5·5 g.) for 5 hours. After removal of the solvent, the ethereal solution of the residue was chromatographed on alumina, but yielded the undecomposed complex (2·0 g.). This was refluxed with potassium hydroxide (4·0 g.) in ethanol (100 ml.) for a further 5 hours. The ethanol was removed under reduced pressure and the residue extracted with ether, washed with water, dried, and chomatographed on alumina. Elution with ether yielded 1·3 g. of a yellow solid, m. p. 184—189°. Repeated crystallisation from ether–light petroleum gave *euphorbenetriol* as colourless needles, m. p. 191—192° (Found: C, 77·6; H, 11·4. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·4%). After crystallisation a yellow oil remained which deposited a few nodules on storage for several weeks but could not be readily crystallised. The oil gave a positive Criegee's test for 1 : 2-glycols (*Ber.*, 1931, **64**, 260). Sublimation of euphorbenetriol at 160° in a high vacuum yielded a small amount of white substance, m. p. 173—174° (Found: C, 77·9; H, 11·7. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·4%).

Ketonoreuphorbenol.—Euphorbenetriol (80 mg.) in acetic acid (8 ml.) was treated with lead tetra-acetate (110 mg.) in acetic acid (10 ml.). After 7 hours at 20° water was added, and the precipitate filtered off, dried, and dissolved in light petroleum (b. p. 50—70°). Elution with the same solvent (200 ml.) through alumina (3 g.) gave traces of resinous material, whilst light petroleum–benzene (1 : 1; 300 ml.) gave a solid which crystallised from methanol to yield *ketonoreuphorbenol* as fine colourless needles, m. p. 120—121°. Sublimation at 100° in a high vacuum gave a solid, m. p. 123—124° (Found: C, 80·3; H, 11·2. $C_{30}H_{48}O_3$ requires C, 81·3; H, 11·3%).

Epoxyeuphorbenyl Acetates.—Perbenzoic acid (0·5 g., 1·1 mols.) in chloroform and euphorbadienyl acetate (1·53 g., 1·0 mol.) were allowed to react for 18 hours at 0°, one mol. of oxygen, as determined iodometrically, being absorbed. The solution was washed with 5% sodium carbonate solution, then water, and dried. Removal of the chloroform under reduced pressure gave an oil which solidified rapidly. Fractiona crystallisation from ethanol on the triangular scheme gave *α-epoxyeuphorbenyl acetate* as colourless needles, m. p. 157°, $[\alpha]_D^{20}$ +5·6° (*c*, 1·1 in chloroform) (Found: C, 79·7; H, 10·8. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). The more soluble fraction gave *β-epoxyeuphorbenyl acetate* as colourless plates, m. p. 143°, $[\alpha]_D^{20}$ −1·5° (*c*, 1·3 in chloroform) (Found: C, 79·2; H, 10·7. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

Diketoeuphorbenol.—Euphorbenyl acetate (3 g.) in glacial acetic acid (350 ml.) was treated during 30 minutes with chromium trioxide (3 g.) in 90% acetic acid (350 ml.), and the solution kept at 40—50° for 5 hours. Methanol was then added, the mixture poured into water (1500 ml.), and the solution extracted with ether. The ethereal solution, washed with sodium hydrogen carbonate and water, gave a dark yellow gum which slowly solidified. The yellow solid (3·2 g.) in light petroleum (b. p. 50—70°) was chromatographed through alumina (100 g.): (i) light petroleum (2·2 l.) and light petroleum–benzene (2 : 1; 1·5 l.) eluted a yellow solid (1·9 g.), m. p. 152—156°; (ii) light petroleum–benzene (1 : 1; 750 ml.) gave a trace of yellow oil, benzene (1 l.) a minute quantity of white solid, m. p. 154—160°, and benzene (2 l.) a trace of oil; (iii) benzene (1 l.) gave an orange solid (60 mg.), m. p. 148—156° which on admixture with the solid from fraction (i) had m. p. 120—126°.

Fraction (i), crystallised twice from methanol, gave *diketoeuphorbenyl acetate* as stout, canary-yellow needles (800 mg.), m. p. 163—164°, $[\alpha]_D^{20}$ −39·8° in chloroform (*c*, 0·86), $\lambda_{max.}$ 272·5 mμ., log ε 3·91 in alcohol (Found: C, 76·9; H, 10·1. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%). Hydrolysis of the acetate (200 mg.) with 8% alcoholic potassium hydroxide (20 ml.) for 3 hours gave a dark red solution, and the product, crystallised once from acetone and water and finally from methanol, gave *diketoeuphorbenol*, m. p. 166—167°, $[\alpha]_D^{20}$ −59° (*c*, 0·6 in chloroform) (Found: C, 78·6; H, 10·5. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

Diketoeuphorbenone.—Diketoeuphorbenol (100 mg.) in benzene (30 ml.) was shaken with a solution of chromium trioxide (150 mg.) in 80% acetic acid (25 ml.) for 30 hours. The product was worked up as for euphorbenone (see above), leaving a yellow solid which was crystallised three times from chloroform–methanol, to give *diketoeuphorbenone* (20 mg.) as canary-yellow needles, m. p. 139°, $\lambda_{max.}$ 269 mμ., log ε 3·93 in alcohol (Found: C, 79·8; H, 10·2. $C_{30}H_{46}O_3$ requires C, 79·2; H, 10·2%). Chromic acid oxidation of euphorbenol in glacial acetic acid at 50° also gave diketoeuphorbenone, m. p. 139°, undepressed on admixture with the above ketone.

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565. *The* Euphorbia *Resins. Part VIII.* Epoxides from, and Oxidations at the Inert Double Bond of, Euphol, Euphorbol, and Tirucallol.*

By J. B. Barbour, R. N. E. Bennett, and F. L. Warren.

The action of perbenzoic acid on euphadienyl, euphorbadienyl, and tirucalladienyl acetates and their dihydro-compounds has given solid epoxides; and per-acid titration may be used to measure unsaturation in these compounds. Euphatriene forms triepoxyeuphane.

The epoxy-derivatives of euphenyl, euphorbenyl, and tirucallenyl acetates gave with concentrated sulphuric acid in acetic acid the dehydro-compounds which contain two conjugated double bonds and which react with only one mole of perbenzoic acid.

Diketoeuphenyl and diketoeuphorbenyl acetates with selenium dioxide give triketoeuphadienyl and triketoeuphorbadienyl acetates.

Euphol (euphadienol) and tirucallol (tirucalladienol) (cf. Haines and Warren, *J.*, 1950, 1562), as well as euphorbol (euphorbadienol) (cf. Barbour, Warren, and Wood, preceding paper) contain an inert double bond situated between two methylene groups, *e.g.*, $\cdot CH_2 \cdot C:C \cdot CH_2 \cdot$. The reducible double bond in euphadienol (cf. Macdonald, Warren, and Williams, *J.*, 1949, S 155; Dupont, Dulou, and Vilkas, *Bull. Soc. chim.*, 1949, **16**, 811) and in tirucalladienol (Haines *et al.*, *loc. cit.*) exists as an *iso*but-1-enyl group, $\cdot CH:CMe_2$, whilst euphorbadienol contains a methylene linkage (Barbour *et al.*, *loc. cit.*).

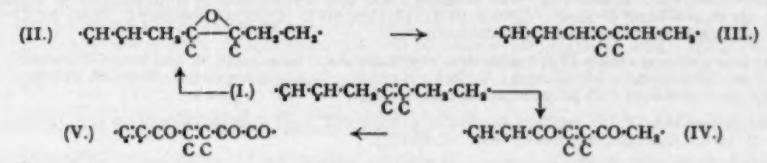
Oxidative degradation of euphadienyl and tirucalladienyl acetates (cf. Bennett, Krusi, and Warren, *J.*, 1951, 2534) with potassium permanganate and chromic acid had resulted in an attack in the neighbourhood of both double bonds. It was felt that the failure after ozonolysis to isolate in reasonable yields the C_{27} compound from euphadienyl acetate (cf. Macdonald *et al.*, *loc. cit.*) and the C_{29} ketone from euphorbadienyl acetate (cf. Barbour *et al.*, *loc. cit.*) was due in part to some oxidation at the inert double bond. A study was therefore made of the action of perbenzoic acid on these three isomeric triterpene acetates with a view to the determination of the relative reactivity of the ethylenic linkages to oxidation and the possible preparation of epoxides which could be used as starting materials for further studies.

It was found that the *iso*butenyl groups in both euphadienyl and tirucalladienyl acetates were very reactive whilst the inert ethylenic bonds in all three triterpenes were slowly attacked. In every case it was possible to isolate the corresponding epoxide, and in this series of triterpenes perbenzoic acid may be used to determine unsaturation. Euphadienyl acetate gave on all occasions a crystalline compound, $C_{32}H_{52}O_3$, m. p. 126—127°, $[\alpha]_D^{20}$ +32·7°, whereas Vilkas, Dupont, and Dulou (*Bull. Soc. chim.*, 1949, **16**, 831) give m. p. 126—127°, $[\alpha]_D$ +35·4°. Euphatriene, prepared by the dehydration of euphadienol (cf. Bennett and Warren, *J.*, 1950, 697), gave triepoxyeuphane. The stability of the epoxide grouping attached to the inert double bond in these three triterpene alcohols is in contrast with that found by Birchenough and McGhie (*J.*, 1949, 2038) for the epoxide of dihydrolanosteryl acetate which Ruzicka, Rey, and Muhr (*Helv. Chim. Acta*, 1944, **27**, 472) showed contained a similar inert ethylenic grouping. The stability of the epoxide grouping was revealed in another experiment. In an attempt to open the ring at the position of the original hydroxyl group, euphenone was treated with perbenzoic acid. No lactone formation could be detected and the product was epoxyeuphanone, identical with the oxidation product of epoxyeuphanol, which was obtained by the hydrolysis of, and which could be reacetylated into, its acetate.

Euphenyl, euphorbenyl, and tirucallenyl acetates gave stable isomeric epoxy-compounds, $C_{32}H_{44}O_3$, which were readily converted by concentrated sulphuric acid in acetic acid into isomeric dehydro-compounds, $C_{32}H_{42}O_3$, formulated as euphadienyl, euphorbadienyl, and tirucalladienyl acetates respectively, which were readily hydrolysed to the corresponding alcohols. These dehydro-derivatives, which were isomeric with euphyl, euphorbyl, and tirucallyl acetates respectively, showed, however, absorption in the ultra-violet indicative of a conjugated system of double bonds. Dehydroeuphenyl acetate in alcohol showed three distinct maxima, at λ 233 (log ε 4·26), 240 (log ε 4·3), and 247·5 mμ. (log ε 4·1) whilst dehydroeuphorbenyl and dehydrotirucallenyl acetates as well as the corresponding alcohols revealed pronounced maxima at the first two wave-lengths. The mode of formation of the dehydro-compounds is

* Part VII, preceding paper.

assumed to be the opening of the epoxy-group (II) to give a ditertiary glycol which then is dehydrated to give (III).



The action of perbenzoic acid on dehydroeuphenyl acetate showed that only one atom of oxygen was absorbed, in which respect it resembles dihydroagnosteryl acetate (cf. Birchenough and McGhie, *loc. cit.*).

Except for the stability of the epoxides, the inert ethylenic linkage in the three triterpenes under discussion is seemingly similarly placed to that in lanosterol. Dorée, McGhie, and Kurzer (*J.*, 1949, 560) were able to effect further oxidation in the neighbourhood of the inert double bond by the action of selenium dioxide on dihydrodiketolanosteryl acetate. This reaction has been reinvestigated by Voser, Montavon, Gunthard, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1950, **33**, 1893) and interpreted in the light of infra-red spectra of the product. The action of selenium dioxide on both diketoeuphenyl and diketoeuphorbenyl acetates, containing the grouping (IV), has given respectively triketoeuphadienyl and triketoeuphorbadienyl acetates, containing the grouping (V), which showed strong absorption in alcohol at $\lambda_{max.}$ 285 mμ. (log ε 4·0 and 3·9 respectively). The properties of these triketones resemble those of triketolanostadienyl acetate and it seems that the carbon atoms in the neighbourhood of the inert double bond are similarly placed. This concept is also in agreement with the hypothesis previously advanced by Haines and Warren (*J.*, 1950, 1562) that the two polar groups in diketoeuphenyl acetate acted in opposite directions.

Dupont *et al.* (*loc. cit.*) drew attention to the seeming identity of bassenyl and euphenyl acetates indicated by mixed melting points. Since basseol has been cyclised by Heilbron, Moffatt, and Spring (*J.*, 1934, 1583) to β-amyrin the disposition of the carbon atoms was assumed to be similar. It is not easy, however, to see how to accommodate the grouping (I) in a structure of euphol based on the accepted formulation of β-amyrin.

Experimental.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.

Formation of Epoxides.—An approximately 5% solution of perbenzoic acid in chloroform was added to the substance at 0° and the mixture set aside. Aliquot portions were withdrawn at intervals and the excess of perbenzoic acid was determined iodometrically. When the theoretical amount of oxygen had been absorbed (see Table) the chloroform solution was shaken three times with 5% sodium carbonate solution, then three times with water and dried (Na_2SO_4). Evaporation of the solvent usually gave an oil which slowly solidified. Unless otherwise stated below, not more than two crystallisations from ethanol sufficed to give the following epoxy-compounds colourless and pure.

Starting material.	Perbenzoic acid (mols.).	Temp.	Reaction time.	Oxygen uptake (mols.).	Product.
Euphadienyl acetate	1·1	0°	4 hours	1	(VIII)
Euphadienyl acetate	2·2	0	—	2	(IX)
Euphenyl acetate	1·1	20	3 days	1	(X)
Euphorbenyl acetate	1·1	0	4 ,,	1	(XI)
Tirucallenyl acetate	1·1	0	8 ,,	1	(XII)
Euphatriene	3·4	20	17 ,,	3	(XIII)
Euphenone	1·0	0	3 ,,	1	(XIV)

Epoxyeuphenyl acetate (VIII), needles, m. p. 126—127°, $[\alpha]_D^{20}$ +32·7° in chloroform (*c*, 1) (Found: C, 79·3; H, 10·9. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

Diepoxyeuphanyl acetate (IX), felted needles, m. p. 180—181°, $[\alpha]_D^{20}$ +57·7° in chloroform (*c*, 1·2) (Found: C, 76·45; H, 10·5. $C_{32}H_{52}O_4$ requires C, 76·7; H, 10·5%).

Epoxyeuphanyl acetate (X), needles, m. p. 176—177°, $[\alpha]_D^{20}$ +59°, giving no colour with tetranitromethane (Found: C, 78·9; H, 11·3. Calc. for $C_{32}H_{54}O_3$: C, 78·9; H, 11·2%). Vilkas *et al.* (*loc. cit.*) give m. p. 178—178·5°, $[\alpha]_D$ +63°. Hydrolysis of the acetate and crystallisation of the product three

times from methanol gave fine white felted needles of *epoxyeuphanol*, m. p. 140—141°, $[\alpha]_D^{20}$ +51·1° in chloroform (*c*, 1) (Found: C, 80·4; H, 11·7. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8).

Epoxyeuphorbanyl acetate (XI) was obtained after five crystallisations from ethanol as colourless plates, m. p. 195—196° (Found: C, 79·8, 79·4; H, 11·2, 10·0. $C_{32}H_{54}O_3$ requires C, 78·9; H, 11·2%). The crystals gave no colour with tetranitromethane.

Epoxytirucallanyl acetate (XII), after two crystallisations from acetone, had m. p. 161—162°, $[\alpha]_D^{20}$ +17·9° in chloroform (*c*, 1·1) (Found: C, 79·1; H, 11·1. $C_{32}H_{54}O_3$ requires C, 78·9; H, 11·2%). The crystals gave no colour with tetranitromethane.

Triepoxyeuphane (VIII), feathery needles, m. p. 161—162°, $[\alpha]_D^{20}$ +46° in chloroform (*c*, 1) (Found: C, 78·5; H, 10·6. $C_{30}H_{46}O_3$ requires C, 78·9; H, 10·6%).

Epoxyeuphanone.—(*a*) Epoxyeuphanol (2·2 g.) in benzene (65 ml.) was added to a solution of chromium trioxide (2·2 g.) in acetic acid (65 ml.) and water (30 ml.), and the whole stirred for 24 hours at room temperature. Methanol was then added, the benzene layer separated, and the aqueous layer run into water and extracted with ether. The benzene and ether solutions were washed with 3% sodium carbonate solution and water and then evaporated under reduced pressure. The product in light petroleum was chromatographed through alumina, to give epoxyeuphanone as a colourless oil (2 g.). *Epoxyeuphanone oxime* crystallised from ethanol in pearly white laminæ, m. p. 188—189°, $[\alpha]_D^{20}$ +56·4° in chloroform (*c*, 1·1) (Found: C, 79·1; H, 11·3; N, 3·2. $C_{30}H_{51}O_2N$ requires C, 78·7; H, 11·2; N, 3·1%).

(*b*) Euphenone was treated with perbenzoic acid (see table above), and the product in light petroleum was filtered through alumina. The colourless oil (XIV), which gave no colour with tetranitromethane, gave an oxime, m. p. 189—190°, undepressed when mixed with epoxyeuphanone oxime (Found: C, 80·3; H, 11·3. Calc. for $C_{30}H_{51}O_2N$: C, 78·7; H, 11·2%)

Dehydroeuphenol (*Euphadienol*).—Epoxyeuphanyl acetate (1·5 g.) in acetic acid (75 ml.) was treated with concentrated sulphuric acid (6 drops) and set aside at room temperature for 24 hours. The product was poured into water and extracted with ether. The ethereal solution, washed successively with dilute sodium carbonate solution and water, was dried (Na_2SO_4) and filtered through activated alumina (10 g.). The solid (1·4 g.) obtained by the evaporation of the ether crystallised from ethanol, to give *dehydroeuphenyl acetate*, m. p. 111—112°, $[\alpha]_D^{20}$ −9·16° in chloroform (*c*, 1), showing $\lambda_{max.}$ 233, 240, 247·5 mμ. (log ε 4·26, 4·3, 4·1 respectively) in alcohol (Found: C, 81·9; H, 10·95. $C_{32}H_{52}O_3$ requires C, 82·0; H, 11·2%). The crystals were coloured reddish-brown with tetranitromethane. Hydrolysis of the acetate with alcoholic potassium hydroxide and crystallisation of the product from methanol gave *dehydroeuphenol*, m. p. 116—117°, $[\alpha]_D^{20}$ −119° in chloroform (*c*, 1), showing $\lambda_{max.}$ 232·5, 240 mμ. (log ε 4·17, 4·21 respectively) in alcohol (Found: C, 84·35; H, 11·75. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). Treatment of dehydroeuphenyl acetate with perbenzoic acid as previously described led to absorption of 1·2 mols. after 7 days at 0°, to give an oil. A solution of the oil in light petroleum was filtered through alumina and the product crystallised from aqueous acetone as fine colourless felted needles, m. p. 234—236°. This was probably epoxydehydroeuphanyl acetate. There was not sufficient for analysis.

Dehydroeuphorbenol (*Euphorbadienol*).—Epoxyeuphorbanyl acetate (400 mg.) in acetic acid (30 ml.) was treated at the b. p. with concentrated sulphuric acid (2 drops) and allowed to cool. The yellow crystalline solid (350 mg.) which separated was filtered off and dissolved in ether. The ethereal solution, washed with sodium carbonate solution, then water and dried, was percolated through activated alumina (20 g.). Ether (50 ml.) eluted a colourless solid which, crystallised six times from methanol, gave *dehydroeuphorbenyl acetate* as colourless plates (38 mg.), m. p. 144—144·5°, $[\alpha]_D^{20}$ −139° in chloroform (c, 0·8), showing light absorption at $\lambda_{max.}$ 232, 239 mμ. (log $\varepsilon_{max.}$ 4·15, 4·19 respectively) in alcohol (Found C, 81·8; H, 11·1. $C_{32}H_{52}O_3$ requires C, 82·0; H, 11·2%). Hydrolysis with 8% alcoholic potassium hydroxide and crystallisation of the product from acetone–methanol gave *dehydroeuphorbenol* as fine needles, m. p. 104°, $[\alpha]_D^{20}$ −136° in chloroform (*c*, 0·9), showing light absorption at $\lambda_{max.}$ 232, 239 mμ. (log $\varepsilon_{max.}$ 4·02, 4·06 respectively) in alcohol (Found: C, 83·2; H, 11·7. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). Both the alcohol and the acetate gave a deep brown colour with tetranitromethane.

Dehydrotirucallenol (*Tirucalladienol*).—Epoxytirucallanyl acetate (600 mg.) was dehydrated as above and the dried yellow ethereal solution percolated through alumina (6 g.). Three crystallisations from acetone–methanol gave colourless hexagonal laminæ of *dehydrotirucallenyl acetate*, m. p. 132—133°, $[\alpha]_D^{20}$—135·5° in chloroform (*c*, 1·06) (Found: C, 82·0; H, 11·2. $C_{32}H_{52}O_3$ requires C, 82·0; H, 11·2%). The crystals showed in alcohol absorption of light at $\lambda_{max.}$ 232·5, 237·5 mμ. (log ε 4·32, 4·31 respectively) and were coloured reddish-brown with tetranitromethane. Similar dehydration of the mother-liquor residues from the purification of epoxytirucallanyl acetate and crystallisation of the resulting product from chloroform–methanol gave flat crystals of dehydrotirucallenyl acetate, m. p. 134—134·5° (Found: C, 82·2; H, 11·1%). The acetate (90 mg.) was refluxed with 5% alcoholic potassium hydroxide (8 ml.) for 2 hours. Two crystallisations of the product from methanol gave regular plates of *dehydrotirucallenol*, m. p. 85—86°, $[\alpha]_D^{20}$ −163·6° in chloroform (*c*, 1·08) (Found: C, 83·6; H, 11·5. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). The crystals showed in alcohol absorption of light at $\lambda_{max.}$ 232·5, 240 mμ. (log $\varepsilon_{max.}$ 4·13, 41·7 respectively), and gave a reddish-brown colour with tetranitromethane.

Triketoeuphorbadienyl Acetate.—Diketoeuphorbenyl acetate (1 g., 1 mol.) in acetic acid–acetic anhydride (1 : 1; 25 ml.) was treated with selenium dioxide (1 g., 4·5 mols.) dissolved in a minimum quantity of water (*ca.* 1 ml.). After the initial ebullition the solution was refluxed for 4 hours, and the cooled solution filtered to remove selenium, poured into water and extracted with ether. The ethereal extract was washed with aqueous sodium hydroxide until no further selenium separated at the

ether–water interface, then with water, and dried. The removal of the solvent under reduced pressure left an orange-yellow solid which was chomatographed on activated alumina (40 g.). Light petroleum (1500 ml.) eluted a yellow solid (350 mg.), m. p. 218°, which was crystallised four times from chloroform–methanol, to give *triketoeuphorbadienyl acetate* as light yellow plates, m. p. 228—229°, which fell to 199—200° on drying at 100° in a high vacuum (Found : C, 74·8; H, 9·1. $C_{32}H_{46}O_5$ requires C, 75·25; H, 9·1%). A further quantity of light petroleum (750 ml.) eluted only a trace of solid. Ether (200 ml.) eluted a dark yellow solid (100 mg.), m. p. 218°, which was crystallised twice from ether to give a further small quantity of impure triketoeuphorbadienyl acetate as stout orange-yellow needles, m. p. 228—229°, which fell to 197—198° on drying at 100° in a high vacuum (Found : C, 74·2; H, 10·9%). Admixture of the two different samples, m. p. 228—229°, showed a m. p. 195—205°, whilst a mixture of the two different samples, m. p. 197—198°, showed no depression.

Triketoeuphadienyl Acetate.—Diketoeuphenyl acetate (3 g.), now obtained with m. p. 110—111° (cf. Macdonald *et al.*, *loc. cit.*; Haines and Warren, *loc. cit.*), was oxidised and worked up as described above. Greater difficulty was experienced in the removal of the selenium. Filtration through alumina (60 g.) with light petroleum as solvent gave deep yellow crystals, m. p. 175—180°, which after two crystallisations from methanol gave *triketoeuphadienyl acetate* as deep yellow needles, m. p. 186°, $[\alpha]_D^{20}$ —16·4° in chloroform (*c*, 1·06) (Found, after drying at 100° and 25° respectively : C, 75·2, 75·0; H, 9·0, 9·0. $C_{32}H_{44}O_5$ requires C, 75·2; H, 9·1%). The crystals on exposure to air or heat at 100° in a high vacuum darkened, but assumed the original yellow colour on storage.

The authors gratefully acknowledge the award of bursaries to two of them (J. B. B. and R. N. E. B.) by the Council for Scientific and Industrial Research, and the assistance of Marjorie von Klemperer (C.S.I.R. Assistant) in spectroscopic determinations.

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566. *Compounds Containing the 2 : 2 : 4-Trimethylhexyl Skeleton. Part I.*

By E. E. Turner and L. Turner.

The synthesis of 2 : 2 : 4 : 7-tetramethyloctane and 6-ethyl-2 : 2 : 4-trimethyloctane and of related compounds is described.

Since the asymmetric carbon atom in 3 : 5 : 5-trimethylhexanol, $CMe_3 \cdot CH_2 \cdot \overset{*}{C}HMe \cdot CH_2 \cdot CH_2 \cdot OH$, is on the one hand attached to a *neo*pentyl group and is on the other in the β-position to a primary alcohol group, this alcohol presents features of considerable interest. It is hoped later to describe the behaviour of the optically active alcohol, but in the present communication we are concerned with a preliminary study of the synthetic uses of the racemic material, supplementary to those reported by Keulmanns, Kwantes, and von Bavel (*Rec. Trav. chim.*, 1948, **67**, 298) and Bruner (*Ind. Eng. Chem.*, 1949, **41**, 2860). The former authors concluded that 3 : 5 : 5-trimethylhexanol, as made by the "oxo" reaction from di*iso*butylene, carbon monoxide, and hydrogen, was free from isomers and this we have confirmed by purifying the alcohol through the hydrogen phthalate : the alcohol obtained was indistinguishable from the commercial material after the latter had been distilled.

The trimethylhexanol is smoothly converted by hot hydrobromic–sulphuric acid into the bromide (compare Bruner, *loc. cit.*), the Grignard reagent from which reacts with acetone to give 2 : 5 : 7 : 7-tetramethyloctan-2-ol. From this alcohol, by dehydration, followed by hydrogenation, 2 : 2 : 4 : 7-tetramethyloctane has been prepared.

3 : 5 : 5-Trimethylhexyl bromide and ethyl sodioacetoacetate give ethyl 3 : 5 : 5-trimethylhexylacetoacetate, convertible in good yield into 6 : 6 : 8-trimethylnonan-2-one and in rather poor yield into 5 : 7 : 7-trimethyloctanoic acid. This acid is alternatively obtainable by reduction of 5 : 7 : 7-trimethyloct-2-enoic acid, the product of heating 3 : 5 : 5-trimethylhexanal with malonic acid and pyridine.

The ethyl ester of 3 : 5 : 5-trimethylhexanoic acid, obtained by oxidising the trimethylhexanol, reacts normally with ethylmagnesium bromide to give 3-ethyl-5 : 7 : 7-trimethyloctan-3-ol, and elimination of water from the latter produces what appears to be a single olefin, which, when catalytically hydrogenated, gives 6-ethyl-2 : 2 : 4-trimethyloctane.

Experiments are in progress on the optical resolution of some of the alcohols and acids.

Experimental.

3 : 3 : 5-*Trimethylhexyl Hydrogen Phthalate*.—A mixture of 3 : 5 : 5-trimethylhexanol (144 g., 1 mole), phthalic anhydride (148 g., 1 mole), and pyridine (79 g., 1 mole) was heated at 100° for 2½ hours. The mixture was poured into excess of dilute hydrochloric acid and the solid collected, ground, and washed with dilute hydrochloric acid. It was dissolved in light petroleum (b. p. 40—60°), and the solution was extracted with water. The solvent was removed and the dried residue was twice crystallised from light petroleum (b. p. 40—60°). The *hydrogen phthalate* had m. p. 52—52·5° (Found : C, 69·3; H, 8·0%; equiv., 292. $C_{17}H_{24}O_4$ requires C, 69·9; H, 8·2%; equiv., 292).

The hydrogen phthalate was hydrolysed in boiling 30% aqueous sodium hydroxide solution, and the product distilled in steam. After separation and distillation a 92% yield was obtained of 3 : 5 : 5-trimethylhexanol, b. p. 192·7°/759 mm. (corr.), n_D^{25} 1·4305 (Found : C, 75·6; H, 13·9. Calc. for $C_9H_{20}O$: C, 75·0; H, 13·9%).

3 : 5 : 5-*Trimethylhexyl Bromide*.—A mixture of trimethylhexanol (576 g., 1 mol.), 48% aqueous hydrobromic acid (1076 c.c., 2·5 mols.) and concentrated sulphuric acid (588 g., 1·5 mols.) was heated for 5 hours at 110°. The bromide layer was dissolved in light petroleum (b. p. 40—60°), and the solution washed with water, concentrated sulphuric acid, water, and finally sodium hydrogen carbonate solution. It was dried azeotropically with benzene and then distilled. The bromide (564 g., 68%) had b. p. 72·5°/12·5 mm., n_D^{25} 1·4516 (Found : C, 52·1; H, 8·6; Br, 38·8. Calc. for $C_9H_{19}Br$: C, 52·2; H, 9·2; Br, 38·7%).

2 : 5 : 7 : 7-*Tetramethyloctan-2-ol*.—Magnesium turnings (13·4 g., 1·1 atoms), activated under ether by means of a trace of iodine, reacted with 3 : 5 : 5-trimethylhexyl bromide (104 g., 1 mol.) at the boiling point of the mixture. When no further change occurred, acetone (30 g., 1 mol.) was added gradually at the ordinary temperature. After 15 hours, aqueous ammonium chloride was added and the ethereal layer separated, washed, and dried. Distillation gave 2 : 5 : 7 : 7-*tetramethyloctan-2-ol* (69 g., 74%), b. p. 85·5—88°/5 mm., n_D^{25} 1·4360 (Found : C, 77·2; H, 13·9. $C_{12}H_{26}O$ requires C, 77·4; H, 14·0%).

2 : 2 : 4 : 7-*Tetramethyloctane*.—The tetramethyloctanol (60 g.) was heated with naphthalene-2-sulphonic acid (0·6 g.). The olefinic *product* (44 g., 81%) had b. p. 71—76°/17 mm. (Found : C, 85·5; H, 14·3. $C_{12}H_{24}$ requires C, 85·7; H, 14·3%). It was hydrogenated in ethyl alcoholic solution at 3—5 atm. pressure in the presence of Adams's platinum oxide catalyst, the product being extracted with concentrated sulphuric acid at 0° and washed with aqueous sodium hydrogen carbonate and with water. The 2 : 2 : 4 : 7-*tetramethyloctane* had b. p. 184·5—184·9°/758 mm. (corr.), n_D^{25} 1·4163 (Found : C, 84·7; H, 15·1. $C_{12}H_{26}$ requires C, 84·7; H, 15·3%).

3 : 6 : 8 : 8-*Tetramethylnonan-3-ol*.—This was obtained from trimethylhexylmagnesium bromide and ethyl methyl ketone in 63% yield; the *alcohol* had b. p. 85—88°/2·8 mm., n_D^{25} 1·4408 (Found : C, 77·8; H, 13·9. $C_{13}H_{28}O$ requires C, 78·0; H, 14·0%).

Ethyl **3 : 5 : 5-*Trimethylhexylacetoacetate*.**—To a boiling solution prepared by using sodium (3·4 g., 1 atom), ethyl alcohol (105 c.c.), and ethyl acetoacetate (22 g., 1 mol.) was added, during 3 hours, 3 : 5 : 5-trimethylhexyl bromide (34 g.). After a further 3 hours' boiling, the alcohol was distilled off and the residue extracted with ether. The extract was washed with sodium hydrogen carbonate, dried, and distilled. *Ethyl trimethylhexylacetoacetate* was obtained in 46% yield; it had b. p. 109°/2 mm., n_D^{25} 1·4389 (Found : C, 69·9; H, 11·1. $C_{15}H_{28}O_3$ requires C, 70·3; H, 10·9%).

5 : 7 : 7-*Trimethyloct-2-enoic Acid*.—A mixture of 3 : 5 : 5-trimethylhexanal (15·3 g., 1 mol.), malonic acid (12 g., 1 mol.), and pyridine (15 c.c.) was heated at 100° for 2·5 hours. The ice-cooled mixture was acidified with dilute sulphuric acid, and the mixture extracted with ether. The ethereal portion was extracted with aqueous sodium hydrogen carbonate, and the aqueous layer acidified and extracted with ether. Distillation gave 5 : 7 : 7-*trimethyloct-2-enoic acid* (8·5 g., 47% yield), b. p. 143—145°/8 mm., n_D^{25} 1·4548 (Found : C, 72·1; H, 10·8. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·8%).

5 : 7 : 7-*Trimethyloctanoic Acid*.—(*a*) Trimethyloctenoic acid was hydrogenated in 95% ethyl alcohol in the presence of Adams's platinum oxide. The *trimethyloctanoic acid*, obtained in 72% yield, had b. p. 100°/1 mm., n_D^{25} 1·4361 (Found : equiv., 188. $C_{11}H_{22}O_2$ requires equiv., 186). The *p-bromophenacyl* ester had m. p. 69° (Found : Br, 20·7. $C_{19}H_{27}O_3Br$ requires Br, 20·9%).

(*b*) A solution of ethyl trimethylhexylacetoacetate (18·5 g.) and potassium hydroxide (22 g.) in ethyl alcohol (45 c.c.) was boiled for 5 hours under reflux. The product was poured into water, and non-acidic material removed by ether extraction. The aqueous portion was acidified and extracted with ether. Distillation of the extract gave 5 : 7 : 7-trimethyloctanoic acid (yield 24%), b. p. 114°/3 mm., n_D^{25} 1·4362 (Found : equiv., 187). The *p*-bromophenacyl ester had m. p. 69° and was identical with the corresponding product from (*a*).

6 : 8 : 8-*Trimethylnonan-2-one*.—Ethyl trimethylhexylacetoacetate (40 g.) was stirred for 30 hours with 5% aqueous sodium hydroxide (400 c.c.). The undissolved material was then extracted with ether, and the aqueous solution acidified with sulphuric acid and distilled in steam. The distillate was extracted with ether, etc. The 6 : 8 : 8-trimethylnonan-2-one (19·5 g., 67% yield) had b. p. 84°/4 mm., n_D^{24} 1·4300 (Found : C, 77·8; H, 12·9. $C_{12}H_{24}O$ requires C, 78·3; H, 13·0%). The *semicarbazone* had m. p. 106° (Found : N, 17·6. $C_{13}H_{27}ON_3$ requires N, 17·4%).

3 : 5 : 5-*Trimethylhexanoic Acid*.—Oxidation of trimethylhexanol with chromic anhydride in aqueous acetic acid gave the hexanoic acid, b. p. 120°/13 mm., n_D^{25} 1·4270 (Found : C, 69·0; H, 11·5. Calc. for $C_9H_{18}O_2$: C, 68·4; H, 11·4%). The *acid chloride* was obtained by using phosphorus pentachloride (yield, 88%); it had b. p. 98°/53 mm., n_D^{25} 1·4350 (Found : C, 61·2; H, 9·6; Cl, 19·9. $C_9H_{17}OCl$ requires

C, 61·2; H, 9·6; Cl, 20·1%). The *ethyl* ester was formed in 84% yield when the acid chloride was added to ethyl alcohol and pyridine. It had b. p. 103°/35 mm., n_D^{25} 1·4177 (Found: C, 70·3; H, 11·7. $C_{11}H_{22}O_2$ requires C, 70·9; H, 11·8%).

3-*Ethyl*-5 : 7 : 7-*trimethyloctan*-3-*ol*.—Ethyl trimethylhexanoate (62 g.) was added to ethereal ethylmagnesium bromide (2·5 mols.) and the product worked up in the usual manner. The alcohol was obtained in 60% yield, and had b. p. 92°/7 mm., n_D^{25} 1·4427 (Found: C, 77·7; H, 13·8. $C_{13}H_{28}O$ requires C, 78·0; H, 14·0%).

6-*Ethyl*-2 : 2 : 4-*trimethyloctane*.—Dehydration of trimethylethyloctanol by distillation with naphthalene-2-sulphonic acid gave an 84% yield of olefin, b. p. 92—93°/27 mm. This was hydrogenated in ethanolic solution at 3—5 atm. (platinum oxide catalyst) whereby 6-*ethyl*-2 : 2 : 4-*trimethyloctane* was obtained; it had b. p. 203·5—203·9°/763 mm. (corr.), n_D^{25} 1·4248 (Found: C, 84·8; H, 15·1. $C_{13}H_{28}$ requires C, 84·8; H, 15·2%).

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BEDFORD COLLEGE, LONDON. [*Received, June 28th*, 1951.]

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567. *Interaction of Alcohols and Boron Trichloride.*

By W. GERRARD and M. F. LAPPERT.

The borate, chloroboronate $BCl(OR)_2$, and dichloroboronite $BCl_2{\cdot}OR$, respectively, were rapidly obtained when the appropriate alcohol (*n*-, *iso*-, and *sec*.-butyl, respectively; 3, 2, and 1 mol. for each alcohol) was mixed with boron trichloride (1 mol.) at low temperature. It is suggested that these products are formed by the broadside 4-centre approaches of reactants. The chloroboronates readily decomposed at room temperature affording the alkyl chloride, the trialkyl borate, and boron trioxide, but the dichloroboronites decomposed much less readily and then gave alkyl chloride, boron trichloride, and boron trioxide. Probable mechanisms are discussed. Proportionation readily occurred between the trichloride and trialkyl borate, the chloro-esters being formed.

Rearrangement to *tert*.-butyl chloride occurred in the decomposition of the *iso*butyl chloro-esters; and *tert*.-butyl alcohol (3 mols.) rapidly gave *tert*.-butyl chloride (3 mols.) and boric acid (1 mol.) when mixed with boron trichloride (1 mol.). Dealkylation of tributyl borates (except *tert*.) by hydrogen chloride was not observed. Even hydrogen bromide reacted but slowly.

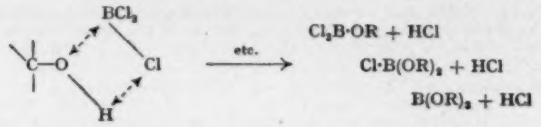
IN a previous paper (*J.*, 1951, 1020) we described experiments on the alcohol–, the alcohol–pyridine–, and the ether–boron trichloride systems with special reference to optically active octan-2-ol and 1-phenylethanol, which were considered as useful standards with respect, not only to the degree of reactivity of the alcoholic carbon atom, but also to the steric course. The function of pyridine was explained, and the preparation of a number of trialkyl borates by means of monopyridinoboron trichloride will be described elsewhere. Extending our observations to mixed ethers of the type of *n*-butyl *sec*.-butyl ether, we found it necessary to have precise information on the related alkyl dichloroboronites $BCl_2{\cdot}OR$, and dialkyl chloroboronates $BCl(OR)_2$.

Apart from work by Wiberg and Sütterlin (*Z. anorg. Chem.*, 1931, **202**, 1, 22, 31), which concerned only methyl and ethyl compounds, manipulated in an enclosed, low-pressure apparatus, and an observation on di*iso*amyl chloroboronate by Kinney, Thompson, and Cheney (*J. Amer. Chem. Soc.*, 1935, **57**, 2396), no information was available to us. We therefore turned to the interaction of the isomeric butyl alcohols with boron trichloride and, although we can now see the need for most detailed and protracted study, we feel it desirable to submit results obtained so far, because of the interest now being shown in esters containing boron (Cook, Ilett, Saunders, and Stacey, *J.*, 1950, 3125) and in the interaction of ethyl alcohol with such chlorides as zirconium tetrachloride (with correlation to the silicon tetrachloride system) (Bradley, Abd-el Halim, and Wardlaw, *J.*, 1951, 280; cf. *Chem. and Ind.*, 1951, 310, and Gerrard, *ibid.*, p. 463).

Addition of boron trichloride (1 mol.) to *n*-, *iso*-, and *sec*.-butyl alcohol (3 mols.) in pentane readily afforded the corresponding trialkyl borate, unaccompanied by alkyl chloride. We

suggest that the stepwise dechlorination proceeds by a four-centre broadside approach (1) rather than by a type of three-centre end-on approach (2):

(1)



(2)

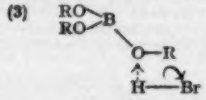
The dechlorination proceeds quickly even at low temperatures, and neither of the intermediate chloro-esters nor the trialkyl borate undergoes dealkylation by hydrogen chloride under the prevailing experimental conditions. Against the inclination to formulate the mechanism as a two-stage one entailing the formation of an addition compound $\begin{matrix}R\\H\end{matrix}\!>\!O\!:\!BCl_3$, followed by decomposition, either by direct expulsion of hydrogen chloride (1) or by extrusion of a proton and a chlorine anion (2), one must consider our observation (*loc. cit.*) that in the co-ordination compound $C_5H_5N\!:\!BCl_3$, the chlorine atoms have much lower reactivity than in the trichloride itself.

Addition of the trichloride (1 mol.) to *tert.*-butyl alcohol (3 mols.) afforded only *tert.*-butyl chloride and boric acid in excellent yield. Here the very reactive alcoholic carbon atom is dominating the situation, and, gleaning information from the 1-phenylethanol example (*loc. cit.*), we suppose a primary formation of some molecules of dichloroboronite, which undergo a S_Ni (Hughes and Ingold) type of decomposition to alkyl halide and BOCl, whereas the latter and hydrogen chloride could react with the alcohol on their own account. Probably a S_N1 mechanism proceeds too; for some loss in optical activity occurred in the 1-phenylethyl system. From experience with the phosphorus trichloride system (Gerrard, *J.*, 1940, 1464; 1944, 85), we suggest the rather unconventional process of a rapid dechlorination to the trialkyl borate, followed by a rapid dealkylation of that by means of hydrogen chloride. The experimental result, however, shows that, in attempting to generalise about an alcohol–non-metallic inorganic halide system from observations with ethanol, one should have regard to the degree of reactivity of the alcoholic carbon atom.

n-Butyl dichloroboronite, $BCl_2{\cdot}OR$, was readily formed in excellent yield by adding the alcohol (1 mol.) to the trichloride (1 mol.). It slowly decomposed at 15°; but there was 81% decomposition in 15·5 hours at 100°, the products being *n*-butyl chloride, boron trichloride, and boron trioxide, indicating an overall equation: $3BuO{\cdot}BCl_2 \longrightarrow 3BuCl + BCl_3 + B_2O_3$. Wiberg and Sütterlin (*loc. cit.*) suggested the intermediate formation of the oxychloride, BOCl, which disproportionated thus: $3BOCl \longrightarrow BCl_3 + B_2O_3$. Having regard to the steric course in the (+)-2-octyl system, in which the alkyl chloride was involved in preponderant inversion plus considerable racemisation, it would appear that the mechanism is not merely the S_N2 one: $RO{\cdot}BCl_2 \longrightarrow Cl^- \dashrightarrow RO{\cdot}BCl^+ \longrightarrow RCl + BOCl$. The S_N1 mechanism $RO{\cdot}BCl_2 \longrightarrow R^+ + BOCl_2^- \longrightarrow R^+ + Cl^- + BOCl \longrightarrow RCl$ probably operates as well, and may even be accompanied by the intramolecular S_Ni mechanism. In a similar way, *iso*butyl dichloroboronite was obtained, and at 100° this decomposed to the extent of 62% in 24 hours; but considerable rearrangement to *tert.*-butyl chloride had occurred. This indicates a hydrogen atom transfer consequent on a S_N1 process. Definite evidence for the formation of *sec.*-butyl dichloroboronite at −80° was secured; but 5 minutes after the cooling-bath had been removed, gelation began, and after 30 minutes decomposition to *sec.*-butyl chloride, boron trichloride, and boron trioxide was well advanced.

Di-*n*-butyl chloroboronate was formed from the alcohol (2 mols.) and trichloride (1 mol.) at −80°; but decomposition to alkyl chloride, trialkyl borate, and boron trioxide readily occurred at 20°, and the overall equation indicated is $3BCl(OR)_2 \longrightarrow 3RCl + B(OR)_3 + B_2O_3$. Di*iso*butyl chloroboronate was formed under similar conditions, and it readily decomposed at 0° giving alkyl (mainly *tert.*-butyl) chloride, tri*iso*butyl borate, and boron trioxide. Evidence for the formation at −80° of di-*sec.*-butyl chloroboronate was similarly secured. It decomposed to *sec.*-butyl chloride, tri-*sec.*-butyl borate, and boron trioxide.

The chloro-esters were readily formed at low temperatures by interaction of the trichloride and trialkyl borate. Results of dealkylation of the tri-esters by means of hydrogen halides are recorded in Table III. Having regard to the steric course in the case of the 2-octyl ester, we suggest the mechanism (3). Except with tri-*tert.*-butyl borate (rapid dealkylation),

(3)  etc. $\longrightarrow$ $Br\longrightarrow R-\underset{H}{\overset{|}{O}}-B(OR)_2 \longrightarrow$

$RBr + HO\cdot B(OR)_2 \longrightarrow$

$3RBr + B(OH)_3$

dealkylation by means of hydrogen chloride was not observed. Attack by hydrogen bromide was slow, but that by hydrogen iodide was much quicker. In contrast with the phosphorous ester–hydrogen halide system, the second and the third dealkylation must have followed the first quickly, because there was no sign of any of the intermediate dealkylated forms.

Data described herein are now available for comparison with those for the phosphorus trichloride–alcohol (Gerrard, *loc. cit.*) and the silicon tetrachloride–alcohol (Gerrard and Woodhead, *J.*, 1951, 519) system.

Experimental.

(Percentage yields are based on the equations stated.)

Trialkyl Borates from Alcohol (3 *mols.*) *and Boron Trichloride* (1 *mol.*).—The trichloride in pentane solution was added to the alcohol in pentane at −10°. After the mixture had been kept for 30 minutes at 15°, all volatile matter was removed at 15 mm., the residue then being weighed and distilled. Results are recorded in the following Table, the borates being characterised by comparison with the completely analysed specimens obtained in a previous investigation (Gerrard and Lappert, *loc. cit.*).

Butyl alcohol.	Weight, g.	BCl_3, g.	Total vol. of pentane, c.c.	Residue, g.	B.p./mm.	n.	Distilled $B(OR)_3$, g.	Boron, %, found.*
n-	3·78	2·0	15	3·87	110°/11	n_D^{17} 1·4118	3·6 (92%)	4·84
iso-	8·9	4·7	30	9·17	96°/12	n_D^{16} 1·4050	8·55 (93%)	4·90
sec.-	10·4	5·4	35	11·2	83°/14	n_D^{19} 1·3974	8·6 (80%) (Repeat, 89%)	4·83

* Calc. for $B(OC_4H_9)_3$: B, 4·70%.

Addition of the trichloride (5·4 g., 1 mol.; in pentane, 10 c.c.) to *tert.*-butyl alcohol (10·4 g.) in pentane (25 c.c.) at −10° caused immediate development of a white precipitate, and there was scarcely any evolution of hydrogen chloride. After the reaction mixture had been kept at 15° for 15 minutes volatile matter was removed at 15 mm. From the solid residue (3·4 g.) a liquid (0·45 g.), b. p. 30—40°/40 mm. (free from boron), probably the alcohol, was obtained, and the final residue appeared to be essentially boric acid (2·8 g., 97% based on the reaction: $BCl_3 + 3ROH \longrightarrow 3RCl + H_3BO_3$). There was no evidence of the formation of tri-*tert.*-butyl borate. The operation then being conducted in xylene (total volume 15 c.c.), in order to isolate *tert.*-butyl chloride, the trichloride (3·6 g.) and alcohol (6·74 g.) afforded a brown gel which changed into a white spongy precipitate overnight. From the mixture, *tert.*-butyl chloride (7·6 g., 90%), b. p. 50—53°, n_D^{18} 1·3872, d_4^{17} 0·832 (Found: Cl, 37·9. Calc. for C_4H_9Cl: Cl, 38·4%), was obtained. In the aqueous washing of the residue, boric acid (1·8 g., 95%) was found.

Interaction of Butyl Alcohols (1 *mol.*) *and Boron Trichloride* (1 *mol.*).—Dropwise addition (1·25 hours) of *n*-butyl alcohol (4·78 g.) in pentane (8 c.c.) to the trichloride (6·0 g.) in pentane (15 c.c.) at −10° caused a vigorous and constant evolution of gas. After 12 hours the mixture was distilled. Boron trichloride distilled constantly with the pentane, and finally *n*-butyl chloride (2·3 g.), b. p. 77—78°, n_D^{19} 1·4030, and a residue (1·4 g.) which contained boron trioxide (0·91 g., by titration) were obtained. In this and later cases, further evidence of the presence of boron trioxide was the hygroscopic nature of the residue, and the evolution of heat on addition of water.

In the absence of solvent, *n*-butyl alcohol (7·0 g.) was added to the trichloride (11·2 g.) at −80°, the outlet of the reaction vessel being attached to absorption tubes containing potassium hydroxide kept at 0°. The reaction vessel was then mechanically shaken for 1·5 hours at 15°; by this time, the absorption tubes contained boron and chlorine equivalent to 3·15 g. of hydrogen chloride (representing 30·5% of total chlorine in the system) and boron trichloride (0·3 g.). *n-Butyl dichloroboronite* remained in the vessel as a colourless liquid (14·7 g., 100%) (Found: Cl, 45·5; B, 7·1%); on distillation, it had b. p. 42°/20 mm. (Found: Cl, 45·6; B, 7·0. $C_4H_9OCl_2B$ requires Cl, 45·8; B, 7·02%). It (5·0 g.) was readily hydrolysed with water to *n*-butyl alcohol (1·82 g., 76%), b. p. 114—115°, n_D^{16} 1·4008.

Addition of *iso*butyl alcohol (5·3 g.) in pentane (10 c.c.) to the trichloride (8·4 g.) in pentane (15 c.c.) at −10°, followed by shaking (30 minutes) and evaporation at 40 mm., gave a residue (11·3 g., 100%) which was mainly *isobutyl dichloroboronite* (Found: Cl, 43·2; B, 7·1%), b. p. 34°/20 mm., n_D^{16} 1·4099, d_4^{20} 1·047 (Found: Cl, 45·3; B, 6·92%).

sec.-Butyl alcohol (4·85 g.) was added to the trichloride (7·7 g., 1 mol.) at −80° as described for *n*-butyl alcohol. Boric acid was not precipitated, but gelation occurred within 5 minutes of removal of the cooling-bath, and after 30 minutes the residue (8·38 g.) was a white spongy mass. Analysis of the

absorption-tube contents showed that hydrogen chloride (2·6 g., 36% of total chlorine present) and boron trichloride (1·25 g.) had been absorbed. At 15°/0·5 mm. a liquid (5·4 g.) passed from the reaction residue into a trap at −80°, and the final residue (2·48 g.) contained boron trioxide (1·7 g. by titration). The distillate (5·4 g.) contained boron and ionisable chlorine equivalent to 0·53 g. of boron trichloride, and after being washed and dried afforded *sec.*-butyl chloride (4·4 g., 73%), b. p. 68°, n_D^{20} 1·3974. To determine whether the dichloroboronite is formed, the reagents (ROH, 1·70 g.; BCl_3, 2·70 g.) were mixed at −80°, and dry nitrogen was passed through the mixture for 15 minutes at −80°. Only hydrogen chloride (0·79 g., 94%) was absorbed in the tube. The residue was immediately hydrolysed in an enclosed system, and from the analysis (Found: Cl, 45·0; B, 6·8%) it appeared that the dichloroboronite had been formed at −80°.

Approximate Rate of Decomposition of n-*Butyl Dichloroboronite.*—As *n*-butyl dichloroboronite tends to undergo decomposition to alkyl chloride, boron trioxide, and boron trichloride, a preliminary investigation was made to define the practical limits of stability. Boron trichloride evolved from the dichloroboronite at 15° and at 100° was measured at specified time intervals. *n*-Butyl dichloroboronite (8·3 g.) (Found: Cl, 45·5; B, 7·1%) was put into a flask fitted with an upright, water-cooled condenser, the outlet of which was connected to an absorption tube containing potassium hydroxide. After 44 hours at 15°, the absorption tube was changed, and by this time 0·032 mol. of boron trichloride had been evolved for 3 mols. of dichloroboronite. The vessel was then kept at 100° for 15·5 hours, and the absorption tube changed at specified time intervals. Results are recorded below:

Time, hours	1·25	2·25	3·5	4·5	6·5	7·9	10·9	15·5
BCl_3, g.	0·139	0·621	1·00	1·23	1·43	1·51	1·54	1·67
BCl_3, mol. per 3 mols. of BCl_2·OBu	0·0657	0·299	0·467	0·648	0·692	0·740	0·763	0·805

Other signs of reaction were the increasing amount of precipitate, and increasing rate of reflux. After 15·5 hours the amount of trichloride evolved corresponded to 81% of the amount required for the reaction $3BCl_2$·OBu ⟶ 3BuCl + BCl_3 + B_2O_3, and the residue on distillation afforded a liquid, b. p. 72—74°, mainly *n*-butyl chloride but containing boron trichloride (10·7%). After being washed and dried, the distillate gave *n*-butyl chloride (4·0 g., 81%), b. p. 76—77°, n_D^{16} 1·4022. The residue (1·5 g.) from the primary distillation contained boron trioxide (1·19 g., 96% by titration).

Decomposition of iso*Butyl Dichloroboronite.*—This dichloroboronite (8·3 g.) was heated at 100° as described for the *n*-butyl compound. Results are recorded in the Table below. On distillation, a liquid

Time, hours	1	2·1	3·2	4·2	5·2	6·1	7·1
BCl_3, g.	0·126	0·147	0·175	0·228	0·433	0·629	0·750
BCl_3, mol. per 3 mols. of BCl_2·OR	0·06	0·07	0·08	0·11	0·21	0·30	0·36
Time, hours	8·4	9·4	12·6	15·9	20·7	24·2	
BCl_3, g.	0·813	0·862	0·954	1·037	1·192	1·298	
BCl_3, mol. per 3 mols. of BCl_2·OR	0·39	0·414	0·46	0·50	0·52	0·62	

(4·5 g.), b. p. 45—65°, and a residue of white powder (1·6 g.) were obtained. The distillate contained dissolved hydrogen chloride and boron trichloride, and these were removed by means of moist lead carbonate. The final liquid had a wide distillation range and was a mixture of *tert.*- and *iso*-butyl chlorides (3·9 g., 79%), b. p. 50—68°, separated into fractions, (i) b. p. 50—53° (1·2 g.), n_D^{16} 1·3900 (Found: *tert.*-butyl chloride, 87%), (ii) b. p. 53—64° (2·4 g.), n_D^{17} 1·3930 (Found: *tert.*-BuCl, 55%), and (iii) b. p. 64—68° (0·3 g.), n_D^{17} 1·3962 (Found: *tert.*-BuCl, 17%). The proportion of the tertiary chloride was determined by means of cold alcoholic potassium hydroxide. Even after being in a similar solution of alcoholic potassium hydroxide for 72 hours, a specimen of *iso*butyl chloride gave only 2·2% of Cl (Calc.: Cl, 38·4%). The residue (1·6 g.) from the primary distillation contained boron trioxide (1·2 g., 97%) as indicated by treatment with water and subsequent titration.

Interaction of n-*Butyl Dichloroboronite and* n-*Butyl Alcohol.*—The alcohol (4·12 g., 1 mol.) was added to the dichloroboronite (8·6 g., 1 mol.) at −80°, effluent gases being trapped as described before. After the apparatus had been at 15° for 18 hours, it was found that hydrogen chloride (1·86 g., 92% based on replacement of one chlorine atom) had been evolved. At 15°/15 mm. volatile matter was removed from the residue (10·7 g.); from the final residue (5·5 g.), tri-*n*-butyl borate (3·95 g., 93%, based on decomposition of the chloroboronate), b. p. 70—80°/0·2 mm. (redistilled, b. p. 119°/18 mm.), n_D^{18} 1·4110 (Found: B, 4·8. Calc.: B, 4·7%), was obtained. The final distillation residue (from the 0·2-mm. distillation) contained boron trioxide (1·33 g., 100% based on decomposition). At 15 mm. the loss in weight was 5·2 g., and the calculated loss, if due to *n*-butyl chloride, from decomposition is 5·1 g. It would appear that the monochloroboronate, $BCl(OR)_2$, is formed, but that it decomposes at room temperature according to $3BCl(OR)_2$ ⟶ $3RCl + B(OR)_3 + B_2O_3$.

*Di-*n-*Butyl Chloroboronate.*—Addition (1 hour) of the alcohol (18·6 g., 2 mols.) to the trichloride (14·8 g., 1 mol.) at −80°, followed by mechanical shaking at 0° for 35 minutes, led to a loss in weight of 9·4 g. [Calc. for hydrogen chloride from 2ROH + BCl_3 ⟶ $BCl(OR)_2$ + 2HCl: 9·2 g.]. There can be little doubt that the residue was a good specimen of *di*-n-*butyl chloroboronate*, n_D^{20} 1·4132 (Found: Cl, 17·7; B, 5·9. $C_8H_{18}O_2ClB$ requires Cl, 18·4; B, 5·65%). To follow the approximate rate of decomposition at 20°, another specimen (16·85 g.), n_D^{20} 1·4141, d_4^{20} 0·941 (Found: Cl, 18·1; B, 5·5%), was prepared and samples were withdrawn from it at intervals during 6 hours in order to determine readily (water) hydrolysable chlorine and boron. The chlorine value fell continuously as shown below, whereas the boron values were, 5·5, 5·7, 5·7, 5·7, 5·7, 5·7, and finally 5·8%.

Time, hours	1·25	2·33	3·60	4·80	5·33	63
Hydrolysable Cl, %	13·8	12·0	9·8	7·3	6·9	0·88
Extent of decomp., %	25	35	47	61	63	95

The final mixture (13·85 g.) was heated under reflux for 2 hours and distilled. *n*-Butyl chloride (5·45 g., 83%), b. p. 76—80°, tri-*n*-butyl borate (4·9 g., 89%), b. p. 80—100°/0·4 mm., and a residue (3·0 g.) which contained boron trioxide (1·65 g., 98%) were obtained. The triester was redistilled, b. p. 108°/10 mm., n_D^{20} 1·4105 (Found: B, 4·8. Calc.: B, 4·7%). After being treated with lead carbonate, the alkyl chloride was redistilled: (i) b. p. 76—76·5/765 mm. (1·2 g.), n_D^{17} 1·4038, d_4^{20} 0·877; (ii) b. p. 76·5—77°/765 mm. (1·8 g.), n_D^{17} 1·4042, d_4^{20} 0·879; (iii) b. p. 77—79°/765 mm. (1·8 g.), n_D^{17} 1·4048, d_4^{20} 0·880.

Interaction of iso*Butyl Alcohol* (2 *mols.*) *and Boron Trichloride* (1 *mol.*).—The alcohol (7·5 g.) was added (35 minutes) to the trichloride (6·0 g.) at −80°, and the mixture kept for 15 minutes with the cooling-bath removed. The residue (10·03 g.; loss in weight, 3·47 g.) (Found: Cl, 20·2; B, 5·9%) was probably mainly the chloroboronate—the loss in weight due to hydrogen chloride evolution should be 3·70 g.

Boron Trichloride (1 *mol.*) *and* sec.*-Butyl Alcohol* (2 *mols.*).—The alcohol (7·6 g.) was added (1 hour) to the trichloride (6·0 g.) at −10°, an absorption tube being attached to the vessel. The latter was then shaken at 15° for 30 minutes; the tube had then absorbed hydrogen chloride (3·1 g., 83%) and boron trichloride (0·5 g., based on titration). On distillation, the residue (10·0 g.) afforded crude *sec.*-butyl chloride (4·25 g., 90%), b. p. 60—70°, b. p. 68°, n_D^{16} 1·4012 (after treatment with lead carbonate), and tri-*sec.*-butyl borate (3·0 g., 76%), b. p. 90—91°/20 mm., n_D^{16} 1·4018 (Found: B, 4·7. Calc.: B, 4·7%), and a residue of boron trioxide (1·34 g., 100%, by titration).

When the alcohol (2·2 g.) was added (15 minutes) to the trichloride (1·75 g.) at −80°, and then nitrogen passed through the mixture for 10 minutes, hydrogen chloride (1·00 g., 94%) was absorbed in the tube attached; the residue was then immediately hydrolysed (Found: Cl, 18·4; B, 5·3. *Di*-sec.-*butyl chloroboronate*, $C_8H_{18}O_2ClB$, requires Cl, 18·4; B, 5·65%).

Decomposition of Diiso*Butyl Chloroboronate.*—This process seemed to involve rearrangement to *tert.*-butyl chloride, and so the titrations to estimate the amounts of readily hydrolysable chlorine were carried out rapidly. Even so, the results must be taken as showing a low limit of the rate. A freshly prepared specimen of the chloroboronate (8·4 g.), n_D^{18} 1·4060, d_4^{20} 0·938 (Found: Cl, 18·4; B, 5·6%), was kept at 0° whilst samples were removed for analysis. The approximate rate of decomposition is indicated below:

Time, hours	0	0·43	0·67	1·43	2·84	18·0
Readily hydrolysable Cl, %	14·3	7·7	6·5	6·5	5·8	3·7
Decomposition, %	22	58	65	65	68·5	80

The remaining liquid (5·25 g.) afforded a mixture of *tert.*- and *iso*-butyl chloride (2·15 g., 86%), b. p. 50—58°, tri*iso*butyl borate (2·0 g., 95%), b. p. 67°/0·5 mm., n_D^{20} 1·4035 (Found: B, 4·8. Calc.: B, 4·7%), and a residue (0·85 g.) containing boron trioxide (0·63 g., 99%). The mixed chlorides gave fractions of b. p. 52—53° (0·8 g.), n_D^{15} 1·3899 (Found: Bu^tCl, 94%), b. p. 53—55° (0·8 g.), n_D^{15} 1·3900 (Found: Bu^tCl, 89%), and b. p. 55—57° (0·26 g.), n_D^{15} 1·3908 (Found: Bu^tCl, 87%), the *tert.*-butyl chloride being determined by hydrolysis in cold 3N-nitric acid followed by titration of the chloride by Volhard's method. A specimen of *iso*butyl chloride was mixed with a similar dilute solution of nitric acid and set aside for 72 hours (Found: Cl, 2·4. Calc.: Cl, 38·4%).

Interaction of Boron Trichloride and Trialkyl Borates.—Tri-*n*-butyl borate (1·88 g., 1 mol.) was added to the trichloride (1·85 g., 2 mols.) at −80°. The product was shaken at 18° for 15 minutes, and then at 18°/15 mm. for 10 minutes. The final residue (3·73 g., 100%) had n_D^{20} 1·4162, d_4^{20} 1·079 (Found: Cl, 44·2; B, 6·85. Calc. for the dichloroboronite, $C_4H_9OCl_2B$: Cl, 45·8; B, 7·0%). It had b. p. 38—40°/20 mm. (constant) and left no residue.

Similarly, tri*iso*butyl borate (1·15 g., 1 mol.) and the trichloride (1·9 g., 2 mols.) afforded a residue (Found: Cl, 44·0; B, 6·8%), which distilled constantly at 36°/20 mm. and left no residue.

From tri-*n*-butyl borate (14·4 g., 2 mols.) and trichloride (3·7 g., 1 mol.) at −80°, the final residue, after being kept at −10°/15 mm. for 15 minutes (18·1 g., 100%), had n_D^{20} 1·4141, d_4^{20} 0·941 (Found: Cl, 18·1; B, 5·15. Calc. for the chloroboronate, $C_8H_{18}O_2ClB$: Cl, 18·4; B, 5·65%). This material decomposed readily as already shown. Similarly tri*iso*butyl borate (6·7 g., 2 mols.) and trichloride (1·7 g., 1 mol.) were mixed at −80°, and thoroughly shaken at −10°/15 mm. for 5 minutes. The resulting chloroboronate (8·3 g., 98%) had n_D^{18} 1·4060, d_4^{20} 0·938 (Found: Cl, 18·4; B, 5·6%), and readily decomposed as shown.

Tri-*sec.*-butyl borate (1·8 g., 1 mol.) was added to boron trichloride (1·8 g., 2 mols.) at −80°. The outlet of the reaction vessel was connected to an absorption tube containing potassium hydroxide. The cooling-bath was then removed, and the mixture allowed to warm to 20°; within 5 minutes a white gel developed and boron trichloride was evolved. The vessel was kept at 20° for 15 hours, boron trichloride (0·62 g.) being collected in the absorption tube. The remainder (3·0 g.) afforded *sec.*-butyl chloride (2·2 g.), b. p. 67—69°, contaminated with boron trichloride and, after treatment with moist lead carbonate, redistillation gave *sec.*-butyl chloride (1·9 g.), b. p. 67·5—68·5°, n_D^{15} 1·4008. The residue (0·74 g.) of the primary distillation contained boron trioxide (0·48 g., 90% based on boron in the system).

Tri-*tert.*-butyl borate (2·62 g., 1 mol.) and the trichloride (1·56 g., 1 mol.) at −80° afforded boron trioxide (0·762 g., 96%) and *tert.*-butyl chloride (2·95 g.), b. p. 50—53°, n_D^{19} 1·3878 (Found: Cl, 38·0. Calc. for C_4H_9Cl: Cl, 38·4%).

Dealkylation by Hydrogen Halides.—Results of the passage of hydrogen halides through the trialkyl borates are recorded below. From *tert.*-butyl borate, there were immediate formation of boric acid and evolution of heat. The *tert.*-butyl chloride (2·7 g., 94%), b. p. 52°, was shaken with lead carbonate to remove dissolved hydrogen chloride, and the pure chloride (2·4 g.) then had b. p. 51°, n_D^{20} 1·3862

No.	Butyl borate.	Weight, g.	HX.	Time of passage, hours.	Temp.	Yield of RX, g. (and b. p.).	Borate recovered: g.	b. p. (mm.).	n_D.	Found: B, %.
1	*n*-	9·1	HCl	8	35°	none	9·0	112°/12	1·4107 (20°)	4·7
2	*sec.*-	5·1	HCl	12 / 30	120 / 15	none	4·9	84°/15	1·3968 (20°)	4·8
3	*iso*-	2·54	HCl	13 / 30	115 / 20	none	2·24	96°/14	1·4059 (16°)	(no residue)
4	*tert.*-	2·38	HCl	½	15	2·4 (51°)	(Residue of boric acid, 0·63 g., 98%)			
5	*n*-	5·5	HBr	15	18	none	5·4	116°/18	1·4115 (18°)	—
6	,,	2·25	HBr	7	115	1·4 (97—100°)	1·35	114°/14	1·4111 (20°)	4·7
7	*sec.*-	2·65	HBr	60	20	4·0 (88—90°)	(Residue, 0·8 g. containing boric acid, 0·65 g.)			
8	*iso*-	2·50	HBr	72	20	none	2·42	96°/14	1·4062 (16°)	—
9	,,	3·80	HBr	16 / 30	115 / 20	1·7 (86—89°)	2·27	96°/15	1·4042 (21°)	—
10	*n*-	5·7	HI	¾	18	1·0 (43°/18 mm.)	4·7	114°/18	1·4108 (20°)	—
11	,,	5·5	HI	4	50	12·7 (130°) *	—	—	—	—
12	*sec.*-	1·8	HI	2	20	2·4 (117—119°)	(Residue containing boric acid, 0·46 g., 96%)			

* Found: I, 69·6. Calc. for C_4H_9I: I, 69·1%.

(Found: Cl, 38·3. Calc. for C_4H_9Cl: Cl, 38·4%). The alkyl bromide in expt. 6 was shaken with lead carbonate, and it then had b. p. 99—100°, n_D^{20} 1·4361. In expt. 9 the alkyl bromide was shaken with lead carbonate before redistillation; it had n_D^{23} 1·4328. There was a primary residue (0·30 g.) of boric acid. In expt. 12, primary distillation afforded a liquid, b. p. 105—120°, and a residue of boric acid (0·46 g., 96%). The liquid was shaken with solid sodium thiosulphate and then redistilled; it had b. p. 117—119°, n_D^{20} 1·4945. Tri*iso*butyl borate (2·65 g.) and hydrogen iodide (12 hours at 20°) afforded unchanged borate (1·32 g., 50%), b. p. 96—97°/14 mm., n_D^{16} 1·4061, but the other material was not identified with certainty.

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568. *Mechanism of the Formation of Dialkyl Alkylphosphonates.*

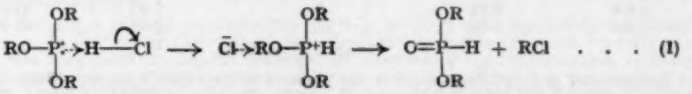
By W. GERRARD and W. J. GREEN.

Interaction of tri-2-octyl phosphite, from (+)-octan-2-ol, and ethyl iodide gave (−)-2-iodo-octane, a result which indicates an intermolecular, end-on, three-centre dealkylation of $EtP(OR)_3^+$ by I^-. Results from the interaction of the same phosphite and acetyl halides indicate the same process: $Ac{\cdot}P(OR)_3^+ + Cl^-$ (or Br^-) ⟶ (−)-2-chloro- and (−)-2-bromo-octane. (+)-2-Iodo-octane was readily, (+)-2-bromo- and (+)-2-chloro-octane were much more slowly, racemised when heated with triethyl phosphite. Observations on (+)-1-halogeno-1-phenylethanes and on tri-1-phenylethyl phosphite are also described. Ethyl dichlorophosphinite did not undergo any clear interaction with ethyl iodide. Overall reaction sequences leading to the formation of alkyl- and acyl-phosphonates are discussed.

By heating triphenyl phosphite with methyl iodide Michaelis and Kähne (*Ber.*, 1898, **31**, 1048) obtained the crystalline compound $PMe(OPh)_3I$, which was easily decomposed by water, according to the equation: $PMe(OPh)_3I + H_2O = Me{\cdot}PO(OPh)_2 + HI + Ph{\cdot}OH$. Landauer and Rydon (*Chem. and Ind.*, 1951, 313) used an alcohol instead of water, and gave an unexpected general method for preparing alkyl iodides. In the preparation of, *e.g.*, diethyl ethylphosphonate by the interaction of triethyl phosphite and ethyl iodide the formation of a similar type of intermediate compound has been assumed, but the compound has not been isolated (Arbusov, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 687). The equation given is $P(OEt)_3 + EtI \longrightarrow PEt(OEt)_3I \longrightarrow EtPO(OEt)_2 + EtI$, and Kosolapoff ("Organophosphorus Compounds," Wiley, New York, 1950) summarises the situation thus: "If the radicals OR [in $Alk{\cdot}P(OR)_3I$] are aliphatic, the intermediate complex breaks down spontaneously, and it is necessary only to distil the mixture to obtain the final product."

The general findings with respect to the nature of the alkyl halide are: ease of reaction is in the order iodide > bromide > chloride, and primary > secondary. Kosolapoff (*op cit.*, and *J. Amer. Chem. Soc.*, 1944, **66**, 109) measured the rate of evolution of ethyl bromide when triethyl phosphite and a bromide such as *n*-butyl bromide were heated together. He concluded that the overall reaction must consist of at least two stages: formation of the intermediate addition compound, followed by its thermal decomposition. Ford-Moore and Williams (*J.*, 1947, 1465) showed that triethyl phosphite and *n*-hexyl bromide (or higher homologues) reacted smoothly and gave mainly ethyl bromide and diethyl alkylphosphonate. With *n*-butyl bromide and *iso*amyl bromide, the reaction was sluggish, and a considerable amount of diethyl ethylphosphonate was formed, because the by-product ethyl bromide had an opportunity to react on its own account. No reaction took place between triethyl phosphite and secondary bromides such as 2-bromo-octane.

We now offer a contribution to the elucidation of the complete sequence of mechanism by considering the dealkylation part of the overall process. Gerrard showed (*J.*, 1944, 85) that 2-chloro-octane was produced by an inversion mechanism during the ready dealkylation of

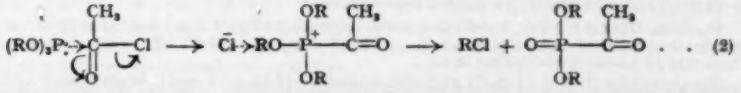


(1)

tri-2-octyl phosphite by hydrogen chloride. The postulated scheme is depicted in (1), and although it is conceivable that the production of the ions could entail two stages [the formation of $(RO)_3P^+HCl^-$, or $HP(OR)_3^+Cl^-$, followed by a S_N1 ionisation] yet it appears certain that dealkylation is not intramolecular; rather is it a process entailing an end-on approach of an anion, the electron affinity of the oxygen atom being increased by the positive charge and thereby encouraging alkyl–oxygen fission. In a general way this picture has long been favoured in the study of the Walden inversion (Lewis, " Valence," Chem. Catalogue, New York, 1923; Kenyon and Phillips, *Trans. Faraday Soc.*, 1930, **26**, 451; Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252). Removal of a second alkyl group by hydrogen chloride is very slow, indicating a less facile mechanism not involving a reactive lone pair of electrons on the phosphorus atom.

Tri-2-octyl phosphite with ethyl iodide at 95—105° afforded 2-iodo-octane, entailing an inversion of configuration. If ethyl iodide is written for hydrogen chloride, scheme (1) will serve to account for this result. There was an experimental complication in that the initially optically pure halide underwent recemisation, probably owing to iodine anionic exchange. When (+)-2-iodo-octane and triethyl phosphite were heated together at 95—105°, the former was quickly racemised, and we attribute this to anionic exchange, $I^- \dashrightarrow R-I \longrightarrow I-R+I^-$, the iodine anions being produced in small concentration by a slow interaction between the phosphite and 2-iodo-octane. The period of heating being increased, the amount of 2-iodo-octane recovered became smaller, and an appreciable amount of diethyl ethylphosphonate was isolated, this having been formed by the ethyl iodide produced by the iodine-anion cycle initiated by the primary interaction between 2-iodo-octane and triethyl phosphite. (+)-2-Bromo- and (+)-2-chloro-octane underwent slow racemisation when heated with triethyl phosphite.

The halogeno-octane formed by the interaction of tri-2-octyl phosphite and the appropriate acetyl halide had also the inverted configuration, and scheme (2) may represent the sequence.



(2)

Whereas (+)-1 chloro- and 1-bromo-1-phenylethane were slowly racemised when heated with triethyl phosphite, the 1-halogeno-1-phenylethane obtained by interaction of tri-1-phenylethyl phosphite and severally ethyl bromide and acetyl chloride was largely racemised. Furthermore, a considerable amount of styrene was produced in this system. The high degree of reactivity of the central carbon atom in the 1-phenylethyl structure dominates the situation here as it does in many other systems.

Just as ethyl dichlorophosphinite undergoes no more than an extremely slow dealkylation by the action of hydrogen chloride, so most of it was recovered after being heated at 70° for 12·5 hours with ethyl iodide. These observations are in accord with the postulations that the

lone pair of electrons on the phosphorus atom are rendered much less available by the electron attraction of the two chlorine atoms.

Experimental.

Rotary powers are for $l = 1$ dm.

Interaction of Tri-2-octyl Phosphite and Ethyl Iodide.—Tri-2-octyl phosphite [9·85 g.; b. p. 162°/2 mm., n_D^{18} 1·4470, α_D^{18} −1·5°; from (+)-ROH, α_D^{20} +7·15°] (Found: C, 68·2; H, 12·1; P, 7·3. Calc. for $C_{24}H_{51}O_3P$: C, 68·8; H, 12·3; P, 7·4%) (cf. Gerrard, *J.*, 1944, 85) was heated at 95—105° with ethyl iodide (3·7 g.) for 4·5 hours. Distillation gave (−)-2-iodo-octane (2·60 g.), b. p. 97°/22 mm., 39—40°/0·5 mm., α_D^{20} −34·4°, and (+)-*di*-2-*octyl ethylphosphonate* (5·97 g.), b. p. 148°/2 mm., $\alpha_D^{17·5}$ +14·16°, n_D^{18} 1·4402 (Found: C, 64·6; H, 11·6; P, 9·3. $C_{18}H_{39}O_3P$ requires C, 64·7; H, 11·8; P, 9·4%). When heating was for 4 hours, the 2-iodo-octane had α_D^{20} −46·0°.

Results for different times of heating are as follows, the other products being unchanged phosphite and the ethylphosphonate:

α_D^{20} for ROH used	$P(OR)_3$, g.	Time of heating (hours)	Yield of RI, g.	I in RI, %*	α_D^{20}
+7·15°	9·85	4·5	2·6	51·0	−34·4°
+7·15	9·85	4	2·3	51·2	−46·0
+8·0	8·36	2	1·67	51·4	−59·3
+8·0	8·36	12	2·65	52·2	−22·2

* Calc.: I = 52·9%.

Racemisation of (+)-2-Iodo-octane in the Presence of Triethyl Phosphite.—When triethyl phosphite (3·5 g., 1 mol.; b. p. 50—51°/15 mm., n_D^{20} 1·4139) (Found: C, 43·3; H, 9·05; P, 18·8. Calc. for $C_6H_{15}O_3P$: C, 43·4; H, 9·1; P, 18·7%) and 2-iodo-octane (5 g., 1 mol.; α_D^{18} +33·6°) were heated together at 100—105° for 8 hours, unchanged triethyl phosphite (2·1 g.), b. p. 51—52°/12·5 mm., and racemised 2-iodo-octane (4·0 g.), b. p. 87—89°/12 mm., α_D^{20} 0·0°, were obtained. Results of other experiments are recorded in the table.

Triethyl phosphite, taken, g.	Triethyl phosphite, recovered, g.	Time of heating (hours)	2-Iodo-octane, taken, g.	2-Iodo-octane, taken, α_D^{20}	2-Iodo-octane, recovered, g.	2-Iodo-octane, recovered, α_D^{20}
1·76	1·70	8	2·5	+33·8°	1·90	0°
1·75	1·52	2·75	2·5	+33·8	2·42	+0·32
1·75	1·62	1·0	2·51	+33·8	2·4	+5·2

After a mixture of triethyl phosphite (3·5 g., 1 mol.) and 2-iodo-octane (0·05 g., 0·01 mol.) had been heated at 100—105° for 8 hours, unchanged triester (2·9 g.), b. p. 47—48°/10 mm., and a fraction (0·2 g.), b. p. 50°/1 mm., probably diethyl ethylphosphonate, were isolated. When a mixture of the triester (3·5 g., 1 mol.) and 2-iodo-octane (0·25 g., 0·05 mol.) was heated at 100—105° for 82 hours, unchanged triethyl phosphite (1·76 g.), b. p. 50—52°/14 mm., and diethyl ethylphosphonate (0·5 g.), b. p. 50°/1 mm., n_D^{20} 1·4165 (Found: C, 43·2; H, 9·2; P, 19·5. Calc. for $C_6H_{15}O_3P$: C, 43·9; H, 9·1; P, 18·7%), were isolated.

Triethyl Phosphite and (−)-2-Chloro- and (−)-2-Bromo-octane.—The triester (3·25 g., 1 mol.; n_D^{15} 1·4170) and (−)-2-chloro-octane (2·9 g.; α_D^{20} −29·7°) were heated at 95—105° for 12 hours. The triester (3·0 g.), b. p. 48—50°/12 mm., n_D^{19} 1·4177, and (−)-2-chloro-octane (2·2 g.), b. p. 57°/12 mm., α_D^{20} −25·0°, n_D^{19} 1·4250 (Found: Cl, 24·4. Calc. for $C_8H_{17}Cl$: Cl, 23·9%), were recovered.

The triester (4·10 g., 1 mol.) and (−)-2-bromo-octane (4·77 g., 1 mol.; α_D^{21} −38·4°) were heated at 95—105° for 12 hours. The triester (3·8 g.), b. p. 51—53°/15 mm., n_D^{17} 1·4175, and (−)-2-bromo-octane (4·54 g.), b. p. 72·5—73°/14 mm., α_D^{20} −35·8°, n_D^{19} 1·4451 (Found: Br, 41·2. Calc. for $C_8H_{17}Br$: Br, 41·4%), were recovered. There was a residue (0·3 g.).

Tri-2-octyl Phosphite and Acetyl Halides.—The triester (12·5 g., 1 mol.; from alcohol, α_D^{20} +8·0°) and acetyl chloride (2·35 g., 1 mol.) were heated at 95—105° for 12·5 hours. No acetyl chloride remained, and from the mixture (−)-2-chloro-octane (4·26 g.), b. p. 57°/13 mm., α_D^{20} −29·64°, n_D^{20} 1·4272 (Found: Cl, 24·2%), and an undistillable residue were obtained.

The same triester (12·5 g., 1 mol.) and acetyl bromide (3·68 g., 1 mol.), heated at 95—105° for 6 hours, afforded (−)-2-bromo-octane (5·33 g.), b. p. 72°/13 mm., α_D^{18} −37·6°, n_D^{19} 1·4495 (Found: Br, 41·4%). There was an undistillable residue (8·8 g.).

Ths phosphite (7·77 g., 1 mol.) and acetyl bromide (2·28 g., 1 mol.), when heated at 95—105° for 12 hours, gave (−)-2-bromo-octane (3·32 g.), b. p. 76·5°/14 mm., α_D^{18} −39·3°, n_D^{18} 1·4480 (Found: Br, 41·3%), and an undistillable residue (5·23 g.).

Interaction of Tri-1-phenylethyl Phosphite and Ethyl Bromide.—The phosphite (Gerrard, *loc. cit.*) (13·1 g., 1 mol.; α_D^{20} +48·0°; from alcohol, α_D^{20} +24·1°) and ethyl bromide (3·5 g., 1 mol.) were heated for 95—105° for 12 hours. Violent refluxing occurred after 2 hours, believed to be due to the formation of styrene. At the end there was a gum and a supernatant liquid which was decanted and distilled. Styrene (3·45 g.), b. p. 39·5—40°/15 mm., n_D^{16} 1·5490 (Heilbron and Bunbury, "Dictionary of Organic Compounds," quote n_D^{20} 1·5462) (which gave the dibromide, m. p. 71—72°), and 1-bromo-1-phenylethane (3·8 g.), b. p. 88·5—89°/15 mm., α_D^{20} +0·8°, n_D^{18} 1·5612 (Found: Br, 43·0. Calc. for C_8H_9Br: Br, 43·3%).

Interaction of Tri-1-phenylethyl Phosphite and Acetyl Chloride.—The phosphite (Gerrard, *loc. cit.*) (10·4 g., 1 mol.; α_D^{20} +48·0°) and acetyl chloride (2·1 g., 1 mol.) were heated at 95—105°. After 30

minutes, a white gummy solid had separated, so heating was discontinued. Distillation of the clear supernatant liquid afforded styrene (0·65 g.), b. p. 35°/14 mm., n_D^{23} 1·5458, 1-chloro-1-phenylethane (6·12 g.), b. p. 76·5°/13 mm., a_D^{18} −20·64°, n_D^{20} 1·5300 (Found: Cl, 25·0. Calc. for C_8H_9Cl: Cl, 25·2%), and an undistillable residue (1·1 g.).

Triethyl Phosphite and (+)-1-*Halogeno*-1-*phenylethane*.—The triester (6·75 g., 1 mol.; n_D^{15} 1·4170) and (+)-1-chloro-1-phenylethane (5·74 g., 1 mol.; a_D^{20} +10·48°) were heated at 95—105° for 13 hours. Unchanged phosphite (5·2 g.), b. p. 48·5—50·5°/13 mm., n_D^{19} 1·4130, and the chloride (5·7 g.) b. p. 74·5—76°/14 mm., a_D^{20} +8·9°, n_D^{17} 1·5290 (Found: Cl, 25·0. Calc. for C_8H_9Cl: Cl, 25·2%), were recovered.

The same triester (8·5 g., 1 mol.; n_D^{15} 1·4170) and (−)-1-bromo-1-phenylethane (9·4 g., 1 mol.; a_D^{22} −17·48°) were heated at 95—105° for 12·5 hours. Distillation then gave unchanged phosphite (5·29 g.), b. p. 50—51°/14 mm., n_D^{15} 1·4151, the bromide (6·47 g.), b. p. 87·5—88·5°/14 mm., a_D^{20} 0·0°, n_D^{20} 1·5230 (Found: Br, 42·9. Calc. for C_8H_9Br: Br, 43·3%), and a fraction (1·97 g.), b. p. 105—106°/0·4 mm., $a_D^{16\cdot5}$ +0·92°, n_D^{16} 1·4961 (Found: C, 59·1; H, 8·0; P, 12·6. *Diethyl* 1-*phenylethylphosphonate*, $C_{12}H_{19}O_3P$, requires C, 59·5; H, 7·9; P, 12·8%).

Triethyl Phosphite and (+)-1-*Chloro*-1-*phenylpropane*.—(+)-1-Chloro-1-phenylpropane (a_D^{16} +53·2°) was heated with triethyl phosphite at 100—105° for 15 hours. The initial mixture of triester (1·66 g., 1 mol.) and alkyl chloride (1·69 g., 1 mol.) had a_D^{20} +24·8°. The rotary powers after the mixture had been heated for specified times were: 15 minutes, a_D^{20} +24·8°; 50 minutes, +25·2°; 2 hours, +25·0°; 6·5 hours, +25·4°; and 15 hours, 25·7°.

On distillation, unchanged triethyl phosphite (0·8 g.), b. p. 47·5°/10 mm., and 1-chloro-1-phenylpropane (1·6 g.), b. p. 46—47°/2 mm., a_D^{24} +41·1°, were isolated. It appears that the concentration of chlorine anion was very small throughout although the slowness of the chlorine-anion exchange process accounts in some measure for the slowness of the racemisation. Octan-2-ol was resolved by Kenyon's method (*J.*, 1922, **121**, 2540), and 1-phenylethanol by that of Houssa and Kenyon (*J.*, 1930, 2260).

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569. *Butadienes and Related Compounds. Part I. Conversion of Asymmetric Di-(p-alkoxyphenyl)ethylenes on Bromination into the Corresponding* 1 : 1 : 4 : 4-*Tetralkoxyphenylbuta*-1 : 3-*dienes.*

By WADIE TADROS and GAMIL AZIZ.

1 : 1 : 4 : 4-Tetralkoxyphenylbuta-1 : 3-dienes are prepared by bromination of the *as*-di-(*p*-alkoxyphenyl)ethylenes, heating the di-*p*-alkoxyphenylvinyl chloride or bromide alone, or heating a mixture of the vinyl bromide and *as*-di-(*p*-alkoxyphenyl)ethylenes. The rôles played by temperature, concentration, and mineral acids are demonstrated. The structure of the butadienes is confirmed by ozonolysis.

IT has been shown [Robson, Schönberg, and Fahim, *Nature*, 1938, **142**, 292; Schönberg, Robson, Tadros, and Fahim, *J.*, 1940, 1327; Schönberg, Robson, and Tadros, *Nature*, 1942, **150**, 22 (Tadros's name was inadvertently omitted from this publication); Tadros and Schönberg, *J.*, 1943, 394; Tadros and Robson, *Nature*, 1947, **160**, 20; Tadros, Farahat, and Robson, *J.*, 1949, 439) that the replacement of the ethylene hydrogen atom in triarylethylenes by halogen was accompanied by a considerable increase in œstrogenic activity. It was hoped that testing the *as*-di-(*p*-alkoxyphenyl)ethylenes and their halogeno-derivatives might throw light on the relation between structure and œstrogenic activity. Tested on groups of 5 ovariectomised mice (average weight, 25 g.), *as*-di-*p*-methoxyphenylethylene and di-*p*-methoxyphenylvinyl bromide (5 mg. in 0·4 c.c. of sesame oil, injected subcutaneously in 4 doses on 2 days) showed practically no activity.

The *as*-diarylethylenes required by us as intermediates were prepared by treating the diaryl ketones with methylmagnesium iodide (cf. Pfeiffer and Wizinger, *Annalen*, 1928, **461**, 132). The required *as*-diarylvinyl bromides were prepared from the diarylethylenes by treatment with one molecular proportion of bromine in acetic acid, chloroform, carbon tetrachloride, or ether, the solutions being warmed only sufficiently to effect dissolution (otherwise the butadienes may be formed) (cf. Pfeiffer and Wizinger, *loc. cit.*; Bergmann and Szmuszkowicz, *J. Amer. Chem. Soc.*, 1947, **69**, 1777).

Bergmann and Szmuszkowicz (*loc. cit.*), by treatment of *as*-di-*p*-methoxyphenylethylene with two atomic proportions of bromine in acetic acid, obtained a compound, m. p. 206—207°, shown later (Bergmann, Szmuszkowicz, and Dimant, *ibid.*, 1949, **71**, 2968) to be 1 : 1 : 4 : 4-

tetra-*p*-methoxyphenylbuta-1 : 3-diene. We have confirmed this result, which we obtained also on use of chloroform or carbon tetrachloride as solvent, and confirmed the structure by ozonolysis of the product to 4 : 4′-dimethoxybenzophenone and glyoxal. Similar preparations gave also the *p*-ethoxy-, *p*-*n*-propoxy-, *p*-*iso*propoxy-, and *p*-benzyloxy-dienes (structures confirmed by ozonolysis), but some dealkylation occurred in the last two cases. Later we found that use of one atomic proportion of bromine gave higher yields of purer products, except in the case of the benzyloxy-compound the yield of which was always low; we hope to discuss the significance of this observation later.

Tetra-*p*-alkoxyphenylbutadienes were also prepared by the following methods: (1) Thermal decomposition of the diarylvinyl chloride or bromide. (2) Refluxing of the *as*-diarylethylene and diarylvinyl bromide in acetic acid; this reaction is autocatalytic, a pronounced induction period being removed by addition of a trace of hydrogen bromide—sulphuric acid is also effective. (3) Refluxing of solutions of the diarylvinyl bromide in acetic acid saturated with hydrogen bromide; a small amount of hydrogen bromide has no effect; the vinyl bromide cannot be replaced by the *as*-diarylethylene which is recovered largely unchanged although the solution acquires a green colour (cf. Schmitz-Dumont, Thömke, and Diabold, *Ber.*, 1937, **70**, 175; Bergmann and Szmuszkowicz, *loc. cit.*). (4) Refluxing of a solution of di-*p*-methoxyphenylvinyl bromide in acetic acid or chloroform containing a little iodine. (5) Treatment of di-*p*-methoxyphenylvinyl bromide with stilbene or 2-phenyl-1 : 1-di-*p*-*iso*propylphenylethylene (Tadros, *J.*, 1949, 442) in acetic acid, which gives the tetra-*p*-methoxyphenyl-diene. Brominated by-products were formed in all cases.

A product, m. p. 149° (Brand and Matsui, *Ber.*, 1913, **46**, 2942; Brand and Kercher, *Ber.*, 1921, **54**, 2007; Brand and Horn, *J. pr. Chem.*, 1927, **115**, 351), supposed to be 1 : 1 : 4 : 4-tetra-*p*-methoxyphenylbuta-1 : 3-diene, appears to differ from the compound, m. p. 206—207°, and this is being investigated. The *p*-ethoxy-diene, m. p. 202°, reported from the same school (Brand, Horn, and Bausch, *ibid.*, 1930, **127**, 240), appears to accord with ours of m. p. 207°.

Reference may be made to the ionic mechanism suggested by Bergmann *et al.* (*locc. cit.*) for the formation of 1 : 1 : 4 : 4-tetra-*p*-methoxyphenylbuta-1 : 3-diene from di-*p*-methoxyphenylethylene by bromine, but comment is reserved.

The formation of butadienes is affected by the temperature and the concentration of the reactants. Thus, equimolecular amounts of bromine and *as*-diarylethylenes, in suspension in a small amount of cold solvent, give the vinyl bromides, whereas from the boiling solutions the butadienes are at once formed. The vinyl bromides could also be obtained when larger amounts of solvent were used. But the butadienes may be formed if escape of hydrogen bromide is prevented; and the effect of iodine is evident from the experiments recorded above. Similarly, *as*-di-*p*-methoxy- and -ethoxy-phenylethylene are largely unaffected by chlorine in small amounts of boiling acetic acid (1 g. of the ethylene in 10 c.c.), but use of larger proportions of the solvent (100 c.c. per g.) leads to 1 : 1-dichloro-2 : 2-di-*p*-ethoxy- and 1 : 1-dichloro-2 : 2-di-*p*-*n*-propoxy-phenylethylene together with unchanged ethylene. Di-*p*-ethoxy- (obtained from 1 : 1-dichloro-2 : 2-di-*p*-ethoxyphenylethane by Brand, *Ber.*, 1913, **46**, 2935) and di-*p*-benzyloxy-phenylvinyl chloride were obtained by chlorination of the ethylene in chloroform or carbon tetrachloride.

Finally, we note that Sheibley and Prutton (*J. Amer. Chem. Soc.*, 1940, **62**, 840) obtained small amounts of 1 : 1 : 4 : 4-tetraphenylbuta-1 : 3-diene and stilbene on bromination of 1 : 1-diphenylethane, the former product doubtless being formed by way of 1 : 1-diphenylethylene.

Experimental.

M. p.s are uncorrected. Microanalyses were by Drs. Weiler and Strauss of Oxford.

as-*Di*-p-*alkoxyphenylethylenes*.—Preparation of these compounds is exemplified by the following. 4 : 4′-Di-*p*-ethoxybenzophenone (15 g.) in ether (250 c.c.) was added to methylmagnesium iodide (from magnesium, 3·4 g., and methyl iodide, 19·8 g.) in ether (150 c.c.), with stirring, during 2 hours and the whole was set aside overnight. The mixture was decomposed with aqueous ammonium chloride and extracted with ether or benzene–ether. Crystallisation from benzene gave *as*-di-*p*-ethoxyphenylethylene (10·6 g.), m. p. 142° (Found: C, 80·3; H, 7·4. Calc. for $C_{18}H_{20}O_2$: C, 80·6; H, 7·5%).

The following were similarly prepared, in 70% yield: as-*di*-p-n-*propoxyphenylethylene*, m. p. 134° (from benzene) (Found: C, 80·8; H, 8·0. $C_{20}H_{24}O_2$ requires C, 81·1; H, 8·1%), as-*di*-*p*-iso*propoxyphenylethylene*, m. p. 54° (from alcohol) (Found: C, 81·6; H, 8·0%), as-*di*-p-*benzyloxyphenylethylene*, m. p. 186° (from acetic acid) (Found: C, 85·6; H, 5·8. $C_{28}H_{24}O_2$ requires C, 85·7; H, 6·1%).

Di-p-*alkoxyphenylvinyl Bromide*.—These were prepared by adding an equimolecular quantity of bromine dissolved in acetic acid, chloroform, carbon tetrachloride, or ether to the *as*-di-*p*-alkoxyphenylethylene dissolved in a comparatively large quantity of the solvent (1 g. of the ethylene in 100 c.c. of

solvent). When acetic acid was used, the mixture was diluted with water and neutralised with sodium carbonate. When other solvents were used, the solutions were shaken with aqueous sodium carbonate, then with water, dried ($CaCl_2$), and filtered, and the solvent was then distilled off. The residues crystallised from alcohol from which they separated in colourless crystals.

Thus were prepared di-*p*-methoxyphenylvinyl bromide, m. p. 84°, di-*p*-ethoxyphenylvinyl bromide, m. p. 64°, *di*-p-n-*propoxyphenylvinyl bromide*, m. p. 42° (Found: C, 64·2; H, 5·9; Br, 21·3. $C_{20}H_{23}O_2Br$ requires C, 64·0; H, 6·1; Br, 21·4%), and *di*-p-*benzyloxyphenylvinyl bromide*, m. p. 119—120° (Found: C, 71·3; H, 4·7; Br, 17·2. $C_{28}H_{23}O_2Br$ requires C, 71·3; H, 4·9; Br, 17·0%).

Di-p-*alkoxyphenylvinyl Chlorides.*—*Di*-p-*benzyloxyphenylvinyl chloride*. A solution of chlorine (0·181 g.) in carbon tetrachloride (3·2 c.c.) was added to a solution of *as*-di-*p*-benzyloxyphenylethylene (1 g.) in the same solvent (150 c.c.) at room temperature. Washing the mixture with aqueous sodium carbonate and then water, and distilling off the solvent, gave an oily residue which crystallised from alcohol. The *vinyl chloride* had m. p. 98—99° (0·92 g.) (Found: C, 78·0; H, 5·0; Cl, 8·8. $C_{28}H_{23}O_2Cl$ requires C, 78·7; H, 5·4; Cl, 8·3%).

The di-*p*-ethoxyphenylvinyl chloride, similarly prepared, had m. p. 76° (from alcohol) (Found: C, 71·5; H, 6·5; Cl, 12·1. Calc. for $C_{18}H_{19}O_2Cl$: C, 71·4; H, 6·3; Cl, 11·7%).

Di-*p*-*n*-propoxyphenylvinyl chloride was obtained only as an oil.

1 : 1-*Dichloro*-2 : 2-*di*-p-*ethoxyphenylethylene*.—Chlorine (0·511 g.) in acetic acid (10 c.c.) was added to a solution of *as*-di-*p*-ethoxyphenylethylene (2 g.) in the same solvent (100 c.c.), and the mixture refluxed for 3 hours, then cooled, diluted with water, and neutralised with sodium carbonate, giving a product of m. p. 132°. This was fractionally crystallised from acetic acid whereby unchanged *as*-di-*p*-ethoxyphenylethylene (0·9 g.), m. p. 142° (not depressed on admixture with an authentic sample), and 1 : 1-dichloro-2 : 2-di-*p*-ethoxyphenylethylene (0·52 g.), m. p. 104—105° [not depressed on admixture with an authentic sample (Fritsch and Feldmann, *Annalen*, 1899, **306**, 72)] (Found: C, 65·0; H, 5·4; Cl, 20·4. Calc. for $C_{18}H_{18}O_2Cl_2$: C, 64·1; H, 5·3; Cl, 21·1%), were obtained.

1 : 1-Dichloro-2 : 2-di-*p*-*n*-propoxyphenylethylene, similarly prepared (0·45 g. from 1 g.), m. p. 78° (from alcohol) [not depressed on admixture with an authentic sample (Stephenson and Waters, *J.*, 1946, 339)] (Found: C, 66·0; H, 5·9; Cl, 19·0. Calc. for $C_{20}H_{22}O_2Cl_2$: C, 65·7; H, 6·1; Cl, 19·4%), was accompanied by 0·11 g. of the unchanged *as*-di-*p*-*n*-propoxyphenylethylene, m. p. 134° (not depressed on admixture with an authentic sample).

1 : 1 : 4 : 4-*Tetra*-p-*alkoxyphenylbuta*-1 : 3-*dienes*.—(*a*) Preparation of 1 : 1 : 4 : 4-tetra-*p*-methoxyphenylbuta-1 : 3-diene by adding bromine (0·6 g., 1 mol.) in acetic (2 c.c.) to boiling solution of the *as*-di-*p*-methoxyphenylethylene (1 g.) in the same solvent (10 c.c.) gave only 0·2 g. (about 20%) of the pure butadiene (contrast Bergmann *et al.*, *loc. cit.*, 1947). Use of chloroform or carbon tetrachloride gave similar results. The solvent was distilled off on the water bath and the residue crystallised from acetic acid from which it separated in pale yellow crystals, m. p. 205—206°. On concentration of the mother-liquor, dark brown brominated by-products were obtained. The experiments were repeated with 0·5 mol. of bromine and only 5 c.c. as a solvent; the yield (0·7 g.) of the pure butadiene was then about 70%. On concentration of the mother-liquor, a little of the brominated by-product was obtained. Either a brown or an olive-green colour developed during the formation of the butadiene.

(*b*) A solution of di-*p*-methoxyphenylethylene (0·48 g., 1 mol.) and di-*p*-methoxyphenylvinyl bromide (0·64 g., 1 mol.) in acetic acid (10 c.c.) was refluxed for 0·5 hour, at the end of which a brown colour developed; on cooling, the butadiene (0·8 g.) was obtained. The butadiene was not formed after 10—15 minutes' refluxing. On the addition of 5 drops of acetic acid containing hydrobromic acid the reaction proceeded at once and the butadiene was formed within 1 minute.

(*c*) Experiment (*b*) was repeated, but without solvent. Evolution of gases started at 160—165° and a brown viscid mass was formed within 10 minutes. Crystallisation from acetic acid gave the butadiene (0·45 g.), m. p. 204—205° not depressed on admixture with an authentic sample.

(*d*) Experiment (*b*), but with stilbene or 2-phenyl-1 : 1-di-*p*-*iso*propoxyphenylethylene (Tadros, *loc. cit.*) instead of di-*p*-methoxyphenylethylene, gave a brown colour after 3 hours' refluxing, but the yield of butadiene was poor.

(*e*) Di-*p*-methoxyphenylvinyl bromide (1 g.) was heated alone. Evolution of hydrogen bromide started at 160—165°, and the mass became dark brown. The pure butadiene (0·21 g.), m. p. 204—205°, was obtained.

(*f*) When a solution of di-*p*-methoxyphenylvinyl bromide (1 g.) in acetic acid (10 c.c.) was boiled there was no change in colour and the vinyl bromide was recovered unchanged. Addition of 5 drops of acetic containing hydrogen bromide in a similar experiment did not alter the result. However, when a solution of the bromide (1 g.) in acetic acid (10 c.c.) saturated with hydrogen bromide was refluxed, a brown colour developed and the butadiene (0·52 g.) was formed within 1 minute.

(*g*) Refluxing a solution of di-*p*-methoxyphenylvinyl bromide (1 g.) in acetic acid (10 c.c.) containing iodine (10 mg.) gave the pure butadiene within 1·25 hours. When iodine (50 mg.) was added, the butadiene (0·3 g.) was obtained within 0·5 hour. In all the above experiments brominated by-products were isolated from the acetic acid mother-liquors after crystallisation. Use of chloroform in the last experiment gave the butadiene within 2 hours.

1 : 1 : 4 : 4-Tetra-*p*-ethoxyphenylbuta-1 : 3-diene, similarly prepared by methods (*a*), (*b*), (*c*), (*e*), (*f*), and (*g*), crystallised from acetic acid in yellow crystals, m. p. 207° (Found: C, 80·8; H, 7·1. Calc. for $C_{32}H_{38}O_4$: C, 80·9; H, 7·1%). Yields corresponded to those obtained above. It was also obtained by heating di-*p*-ethoxyphenylvinyl chloride (0·5 g.) alone at 200—220° for 10 minutes.

1 : 1 : 4 : 4-*Tetra*-p-n-*propoxyphenylbuta*-1 : 3-*diene*, prepared by methods (*a*) and (*c*) and similarly crystallised, formed pale yellow crystals (*ca.* 15—20%), m. p. 198—199° (Found: C, 81·4; H, 7·6. $C_{40}H_{46}O_4$ requires C, 81·4; H, 7·8%).

1 : 1 : 4 : 4-*Tetra*-p-iso*propoxyphenylbuta*-1 : 3-*diene*, prepared as in (*a*) and (*e*), was contaminated with dealkylated products which were separated by treatment with sodium hydroxide solution. It crystalllised from acetic acid in yellow crystals (about 40%), m. p. 187—188° (Found: C, 81·2; H, 7·5%).

1 : 1 : 4 : 4-*Tetra*-p-*benzyloxyphenylbuta*-1 : 3-*diene* was obtained, contaminated with dealkylated products which were separated as above, on addition of bromine (0·42 g.) in acetic acid (2 c.c.) to *as*-di-*p*-benzyloxyphenylethylene (2 g.) suspended in the same solvent (5 c.c.) at the b. p. Boiling was continued for 20 seconds. The diene crystallised from acetic acid in pale yellow crystals (*ca.* 8%), m. p. 225° (Found: C, 85·5; H, 5·9. $C_{56}H_{46}O_4$ requires C, 85·9; H, 5·9%).

When equimolecular quantities of bromine were added to the *as*-di-*p*-alkoxyphenylethylenes suspended in acetic acid (10 c.c.) at room temperature, a mixture of unchanged ethylene and vinyl bromide, which could be separated by fractional crystallisation, was obtained.

Ozonolyses.—A stream of dry ozonised oxygen (3%) was passed through a cold solution of the butadienes in carbon tetrachloride until the reaction was almost complete. Raney nickel sludge (5 g.) in distilled water was added and the mixture warmed on the water-bath for 10 minutes and filtered (cf. Cook and Whitmore, *J. Amer. Chem. Soc.*, 1941, **63**, 3540). The aqueous layer which contained nickel chloride was treated with 2 : 4-dinitrophenylhydrazine in hydrochloric acid (1 : 1), and the glyoxal bis-2 : 4-dinitrophenylhydrazone thus formed was filtered off. It crystallised from nitrobenzene in orange crystals, m. p. 318° alone or mixed with an authentic sample. The carbon tetrachloride layer was washed twice with water, then distilled on the water-bath after addition of distilled water. The residue was extracted with water from which another crop of dinitrophenylhydrazone could be obtained. The di-*p*-substituted benzophenone which did not dissolve in hot water crystallised from alcohol or acetic acid. No other products could be isolated. The following di-*p*-substituted benzophenones were obtained on ozonolysis of the corresponding butadienes: 4 : 4′-dimethoxy-, m. p. and mixed m. p. 142° (3·1 g. from 4 g.), 4 : 4′-diethoxy-, m. p. and mixed m. p. 131° (1·5 g. from 2 g.), 4 : 4′-di-*p*-*n*-propoxy-, m. p. and mixed m. p. 127° (0·7 g. from 1 g.), 4 : 4′-di*iso*propoxy-, m .p. and mixed m. p. 72° (0·75 g. from 1 g.), and 4 : 4′-di-*p*-benzyloxy-benzophenone, m. p. and mixed m. p. 188° (0·7 g. from 1 g.).

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570. *Non-catalytic Reduction of Thiophens. Part I. Thiophen.*

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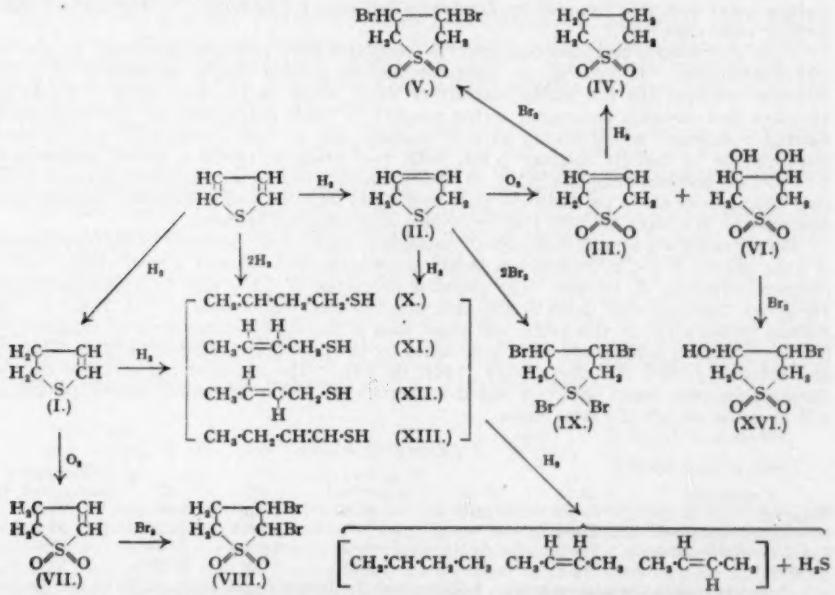
The non-catalytic reduction of thiophen in liquid ammonia by sodium in the presence of methanol yields the isomeric dihydrothiophens as primary products. Concomitant reactions give *n*-butenethiols as secondary and *n*-butenes and hydrogen sulphide as end-products. The structure of the hitherto unknown dihydrothiophens has been established by oxidation to known sulphones; a number of derivatives have been prepared. The presence of three of the four possible *n*-butenethiols in the reaction products was demonstrated by infra-red spectroscopic analysis, genuine specimens of these thiols being synthesised for comparison.

UNTIL recently, attempts to hydrogenate thiophen by the usual hydrogenation procedures using metallic catalysts such as nickel, platinum, and palladium invariably failed, presumably owing to the powerful poisoning effect of this type of sulphur compound. More success, however, attended the use of hydrogenation–dehydrogenation catalysts of the metallic sulphide type. Moldavski and Propopchuk (*J. Appl. Chem. Russia*, 1932, **5**, 619), using a molybdenum sulphide catalyst, found that thiophen was converted into thiophan and butanethiol at 350°, and Moldavski and Kumari (*J. Gen. Chem. Russia*, 1934, **4**, 298) isolated butane and hydrogen sulphide, as well as the products mentioned above, as was confirmed by Cawley and Hall (*J. Soc. Chem. Ind.*, 1943, **62**, 116). More recently, Mozingo *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 2092) successfully hydrogenated thiophen to thiophan over a palladium catalyst, with a very high catalyst-to-thiophen ratio to overcome the poisoning effect. No intermediate products were reported. Fricke and Spilker (*Ber.*, 1925, **58**, 24, 1589) showed that reduction of thionaphthen in boiling ethanol with sodium gave as main product *o*-ethylthiophenol together with an appreciable amount of dihydrothionaphthen. They suggested that the yield of the latter might be greater at a lower temperature but did not confirm this. Since reduction of certain aromatic hydrocarbons in liquid ammonia by means of sodium and methanol has been shown by Wooster and Godfrey (*J. Amer. Chem. Soc.*, 1937, **59**, 596) to yield the corresponding *cyclo*hexadienes in excellent yields, it was considered that the reduction of thiophen

in liquid ammonia offered a possible route to the hitherto unknown dihydrothiophens. The method was accordingly investigated.

The reduction of thiophen in liquid ammonia solution at −40° with sodium in the presence of methanol proceeded readily and smoothly. Preliminary experiments showed that the reaction products consisted of unchanged thiophen, a neutral, higher-boiling fraction, some unsaturated thiol, and butenes and hydrogen sulphide (*Nature*, 1950, **165**, 899). In these experiments sodium equivalent to two molecules of hydrogen per molecule of thiophen was used, resulting in a relatively high yield of thiols, butenes, and hydrogen sulphide. By halving the proportion of sodium used, an enhanced yield of the higher-boiling neutral fraction was obtained which, when the accumulated product from several runs was fractionated, yielded two distinct compounds identified through their derivatives as 2 : 3- (I) and 2 : 5-dihydrothiophen (II). During this fractionation some polymerisation occurred and a relatively large high-boiling residue remained. For this the 2 : 3-dihydrothiophen was eventually shown to be responsible, readily undergoing polymerisation on prolonged heating at atmospheric pressure. Subsequent distillations were carried out at reduced pressure in an atmosphere of nitrogen, polymerisation then being largely avoided.

No evidence was obtained for the addition of a second hydrogen molecule to the remaining ethylenic linkage to yield thiophan. Instead, hydrogenolysis of the ring took place, yielding a mixture of butenethiols which were further reduced to hydrogen sulphide and a mixture of *n*-butenes. Variation in the proportion of sodium used only altered the relative proportions of the various products, optimum yields (*ca.* 40%) of the dihydrothiophens being obtained by using sodium equivalent to one molecule of hydrogen per molecule of thiophen. In the absence of methanol, the reduction proceeded entirely to the thiol stage and beyond, and no intermediate dihydrothiophens were isolated. Variation in the quantity of sodium used led only to a corresponding variation in the ratio of unchanged thiophen to thiol in the product. The reduction of thiophen, with sodium in methanol solution alone, proceeded along the same general route as when ammonia was present but the rate of reaction was much slower.



Although the sulphones corresponding to both dihydrothiophens are known ("Sulfolenes") only one reference to the preparation of a dihydrothiophen was found. Slobodin (*J. Gen. Chem. Russia*, 1938, **8**, 714) claimed to have obtained 2 : 5-dihydrothiophen, amongst other products (including rubber-like polymers, tars, and butadiene), by the action of an

aqueous-alcoholic solution of sodium sulphide on 1 : 4-dibromobut-2-ene. The supposed dihydrothiophen was obtained from the tar, by distillation, as an oil, b. p. 103—105°, n_D^{21} 1·4814, d_D^{21} 0·978. The mercuric chloride complex and methiodide are reported as melting at 92—94° and 122—123°, respectively. Since both dihydrothiophens described in the present work boil appreciably higher and possess much higher refractive indices, there can be little doubt that Slobodin's compound was not a dihydrothiophen. When the physical properties of the material are compared with those of other sulphur compounds boiling in the same range, and Winstein and Young's work (*J. Amer. Chem. Soc.*, 1936, **58**, 104) on the isomerisation of alkenyl bromides is borne in mind, it appears likely that his compound was vinylthiairane (XIV) or some such similar compound formed as follows :

$$Br{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2Br \longrightarrow Br{\cdot}CH_2{\cdot}\underset{Br}{CH}{\cdot}CH{:}CH_2 \xrightarrow{Na_2S} H_2C\!\!<\!\!\begin{matrix}CH{\cdot}CH{:}CH_2\\ S\end{matrix}$$

(XIV.)

The identification of the two isomeric dihydrothiophens followed from their conversion into known sulphones. The sulphone (III) of 2 : 5-dihydrothiophen has been prepared by Staudinger (B.P. 361,341/1930) and by many other workers, including Zuydewijn (*Rec. Trav. chim.*, 1937, **56**, 1047; 1938, **57**, 445) by 1 : 4-addition of sulphur dioxide to butadiene. Zuydewijn characterised his product by reduction of thiophan sulphone (IV) and by conversion into the dibromide (V) (cf. Staudinger and Ritzenthaler, *Ber.*, 1935, **68**, 455) by the addition of bromine in carbon tetrachloride solution. Some difficulty was at first experienced in crystallising the sulphone from 2 : 5-dihydrothiophen but this was eventually traced to the presence of the diol (VI) which resulted from the use of an excess of peroxide. Both sulphone and diol, after purification, had melting points corresponding to Zuydewijn's preparation, as did the dibromide derived from the sulphone. The sulphone (VII) of 2 : 3-dihydrothiophen was obtained by Zuydewijn (*loc. cit.*) from the 2 : 5-derivative by isomerisation in aqueous alkali under the influence of ultra-violet light. The thiophen-derived product agreed in melting point with that recorded by Zuydewijn and gave a dibromide (VIII) of slightly higher melting point than his.

Both methiodides and mercuric chloride complexes were prepared from each of the two dihydrothiophens; in general, 2 : 5-dihydrothiophen yielded stable derivatives of simple structure whereas the few stable derivatives which could be prepared from 2 : 3-dihydrothiophen had complex structures, owing possibly to some polymerisation occurring during reaction. Bromine added readily to both isomers, and 2 : 5-dihydrothiophen gave a stable tetrabromide of definite melting point, with two ionisable bromine atoms, undoubtedly 1 : 1 : 3 : 4-tetrabromothiophan (IX). 2 : 3-Dihydrothiophen in similar circumstances added only two bromine atoms per molecule, yielding a highly unstable, yellow solid which immediately decomposed to a black tar with copious evolution of hydrogen bromide.

Both isomers are colourless liquids of unpleasant odour, but whereas 2 : 5-dihydrothiophen is quite stable, 2 : 3-dihydrothiophen slowly polymerises and deposits a hard yellow solid of complex structure on storage. The physical properties of 2 : 3- and 2 : 5-dihydrothiophen are given, together with those of thiophen and thiophan for comparison, in Table I. The melting points given in this table, and those used in the experimental work to calculate the purities of certain compounds, were determined by the procedure described by Mair, Glasgow, and Rossini (*J. Res. Nat. Bur. Stand.*, 1941, **26**, 591). The chemical properties of the two dihydrothiophens, which are very reactive chemically, with pronounced olefinic behaviour, will form the subject of a later paper.

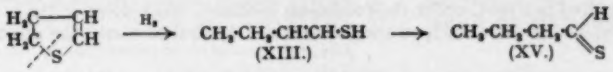
TABLE I.

Compound.	B. p.	M. p.	M. p. for zero impurity.[b]	n_D^{20}.	d^{20}.	Estimated purity, mol. %.
Thiophen	84·0°	− 38·7°[a]	− 38·2°	1·5286	1·0642	99·5
2 : 3-Dihydrothiophen ...	112·0	−110·2	−108·7	1·5311	1·0361	97·5
2 : 5-Dihydrothiophen ...	122·3	− 50·3	− 49·3	1·5306	1·0591	98·5
Thiophan	121·2	− 96·2[a]	− 96·1	1·5047	0·9998	99·7

[a] Determined in these laboratories. [b] Extrapolated value (for significance, see Taylor and Rossini, *J. Res. Nat. Bur. Stand.*, 1944, **32**, 197). [c] Calculated on an assumed value of the cryoscopic constant.

The complete identification of the unsaturated thiol formed by further reduction of the dihydrothiophens proved difficult. Apart from the extremely objectionable odour of these thiols, they easily polymerise to high-boiling, dense, yellow oils (cf. von Braun and Plate, *Ber.*,

1934, **67**, 281). The most satisfactory approach was by comparison of the infra-red absorption spectrograms of the various samples of unsaturated thiols obtained, with those of synthetic butenethiols.* Since these compounds polymerise rapidly when heated, all distillations were carried out at low temperature under reduced pressure, and all samples were examined when freshly prepared and distilled. The general properties of the thiophen-derived thiols were in good agreement with those described by von Braun and Plate (*loc. cit.*). Synthetic samples of but-3-enethiol (X) and both *cis*- and *trans*-but-2-enethiol (XI and XII) were prepared by the action of thiourea on the corresponding bromide. The appropriate butenyl 2 : 4-dinitrophenyl sulphides were prepared from the thiols and appear to offer the most reliable chemical means of characterisation. The fourth possible isomer, but-1-enethiol (XIII), has not been



synthesised, but Campaigne's review (*Chem. Reviews*, 1946, **39**, 1) suggests that it would immediately isomerise to thiobutaldehyde (XV) which would then polymerise to a more complicated molecule. If the cleavage of the 2 : 3-dihydrothiophen occurred as shown below then such a series of reactions would probably take place.

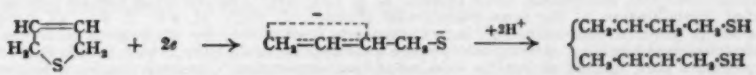
The thiol obtained *directly* from thiophen, by use of a molecular excess of sodium, failed to yield a solid derivative. Examination of the infra-red absorption spectrogram confirmed the presence of approximately 15% of but-3-enethiol (absorption peaks at 10·1 and 10·9 μ.), and 5—10% of *trans*- (peak at 10·4 μ.) and 30% of *cis*-but-2-enethiol (peak near 13·5 μ.). There were indications of the presence of a small quantity of material which had high general absorption above 13 μ. which is thought to be indirectly due to but-1-enethiol.

Both isomeric dihydrothiophens were reduced to the thiol by the action of sodium equivalent to one molecule of hydrogen per molecule of dihydrothiophen, and the products were examined chemically and spectroscopically.

The thiol from 2 : 5-dihydrothiophen yielded a solid butenyl 2 : 4-dinitrophenyl sulphide, m. p. 56—56·5° (after repeated crystallisation from alcohol), which did not depress the melting point of but-3-enyl 2 : 4-dinitrophenyl sulphide (m. p. 57°). Spectroscopic examination confirmed the presence of at least 30% of but-3-enethiol and revealed that about 55% of *cis*- but essentially no *trans*-but-2-enethiol was present.

The thiol from 2 : 3-dihydrothiophen yielded only a liquid derivative, and the spectrogram showed the presence of about 15—20% of but-3-enethiol, only a little *cis*-, and no *trans*-but-2-enethiol. The sample contained a substantial amount of the material of high general absorption above 13 μ. which is believed to be indirectly due to but-1-enethiol.

From these results, it is apparent that some degree of isomerisation occurs when the dihydrothiophens are reduced by sodium and methanol in liquid ammonia. The exact mechanism by which this takes place is not clear, but the work of A. J. Birch (*Quart. Reviews*, 1950, **4**, 69), on the reduction of organic compounds by metal–ammonia solutions, offers a possible explanation. The addition of two electrons to the dihydrothiophen nucleus gives rise to a charged transition complex, *i.e.*, a mesomeric anion, which is then stabilised by proton addition (the methanol acting as proton donor). Proton addition occurs at points of greatest charge stability, the governing factor of which is molecular structure. By this means, but-3-enethiol as well as the Δ^2-isomer could be formed from 2 : 5-dihydrothiophen :



The last stage of the non-catalytic reduction of thiophen is the formation of *n*-butenes and hydrogen sulphide. Since the presence of large quantities of ammonia made this particular stage of the reduction rather difficult to investigate, samples of thiol directly from thiophen and also from each of the dihydrothiophens were caused to react with sodium in refluxing alcohol. The low-boiling hydrocarbon products were collected in a suitable cold trap and analysed. The residual alkaline solution was rich in sodium sulphide and, on acidification to recover unchanged thiol, much hydrogen sulphide was evolved.

* These spectrograms are being submitted for inclusion in the A.P.I. Project No. 44, U.S. Bureau of Standards Catalogue of Infra-red Spectrograms, and so are not shown here.

The thiol from 2 : 3-dihydrothiophen yielded only a negligible amount of butenes, and a large proportion of the non-thiol material recovered consisted of a high-boiling *neutral* oil of

TABLE II.

Component.	Weight % of hydrocarbon product. Thiol direct from thiophen.	Thiol from 2 : 5-dihydrothiophen.
But-1-ene	27·4	23·2
cis-But-2-ene	51·5	76·0
trans-But-2-ene	25·1	0·8

unpleasant odour. This again might be an indirect result of the formation of but-1-enethiol. It must be pointed out that, under the conditions specified, break-down of the other two thiol samples was limited to about 25% of the theoretical. Analytical results are given in Table II.

EXPERIMENTAL.

(Analyses are by Weiler and Strauss, Oxford. All m. p.s and b. p.s are corrected.)

Preparation of Dihydrothiophens.—Thiophen (420 g., 5 mols.) and methanol (1·5 l.) were placed in a 5-l. three-necked flask fitted with a sealed stirrer, toluene thermometer, and solid carbon dioxide reflux-trap to which a vent-line was attached. The flask and its contents were cooled to −40°, and liquid ammonia (*ca.* 1·5 l.) blown in. Sodium (253 g., 11 mols.) was then added in small pieces to the cooled, stirred solution during 8 hours, after which the product was allowed to warm to room temperature overnight to evaporate off the ammonia. The reaction mixture was then carefully diluted with ice-water (2·5 l.) during vigorous stirring while the temperature was kept below 20°, and the resultant aqueous alkaline solution was extracted with *iso*pentane to remove unchanged thiophen and neutral reaction products, and finally acidified with dilute hydrochloric acid whilst being cooled. The liberated thiol separated as an oil which was extracted with *iso*pentane, and the solvent was removed to leave crude butenethiol (71 g., 17%), b. p. 14—16°/20 mm. (101—103°/760 mm.), n_D^{20} 1·4735 (Found : C, 54·4; H, 9·5; S, 35·4. Calc. for C_4H_8S : C, 54·5; H, 9·1; S, 36·4%). The butenyl 2 : 4-dinitrophenyl sulphide from this sample was an oil which could not be induced to crystallise. The neutral product, fractionated through a 20-plate glass-packed column at reduced pressure under an atmosphere of nitrogen, yielded unchanged thiophen (128 g.) and crude dihydrothiophens (164 g., 39%). The accumulated crude product from three such runs was fractionated, yielding 2 : 3-*dihydrothiophen* (12·3%), b. p. 112·0°/760 mm., n_D^{20} 1·5311, d_D^{20} 1·0361 (Found : C, 55·7; H, 7·3; S, 36·5. C_4H_6S requires C, 55·8; H, 7·0; S, 37·2%), and 2 : 5-*dihydrothiophen* (26·2%), b. p. 122·3°/760 mm., n_D^{20} 1·5306, d_D^{20} 1·0591 (Found : C, 56·0; H, 7·3; S, 36·1%).

2 : 5-Dihydrothiophen yielded a *mercuric chloride* complex (from ethanol), m. p. 128° (Found : C, 21·7; H, 3·0; S, 13·6; Cl, 15·2. $2C_4H_6S,HgCl_2$ requires C, 21·65; H, 2·7; S, 14·45; Cl, 16·0%). A mixed m. p. with the corresponding derivative (m. p. 127—128°) of thiophan gave a depression of 8°. The *methiodide* crystallised from ethanol in colourless needles, m. p. 147° (sealed tube) (Found : C, 27·2; H, 4·1; S, 13·9; I, 55·3. C_5H_9SI requires C, 26·4; H, 4·0; S, 14·05; I, 55·6%). Drop-wise addition of bromine to a solution of 2 : 5-dihydrothiophen (8·6 g.) in *iso*pentane (150 ml.) continuously precipitated a yellow powder until the permanent red colour of bromine indicated the end-point of the reaction. The weight of bromine added (33 g.) indicated that four atoms of bromine were absorbed per molecule, and the addition compound (34 g., 85%) recrystallised from carbon tetrachloride as orange crystals, m. p. 101—102° (decomp.). These crystals were relatively stable and gave off only traces of hydrogen bromide after exposure to air for some weeks. The addition compound is undoubtedly 1 : 1 : 3 : 4-*tetrabromothiophan* (IX) (Found : C, 12·2; H, 1·8; S, 7·7; Br, 78·4. $C_4H_6SBr_4$ requires C, 11·8; H, 1·5; S, 7·9; Br, 78·8%). Titration of an aqueous-alcoholic solution against silver nitrate solution showed there to be two ionisable bromine atoms per molecule [Found : Br, 40·5. $C_4H_6SBr_4$ (IX) requires Br^-, 39·4%].

2 : 3-Dihydrothiophen yielded a *mercuric chloride* complex (from ethanol) which was resolved into an ethanol-insoluble, amorphous, white powder, m. p. 130—131°, and colourless needles melting, after repeated crystallisation, at the same temperature (Found : C, 22·2; H, 4·3; S, 8·1; Cl, 9·2%). A mixed m. p. gave no depression and both compounds were shown by analysis to have the same complex empirical formula. Attempts to prepare a methiodide in the normal way, in refluxing ethanol, only yielded a dark viscous oil but, by working at low temperature, colourless needles were obtained, having m. p. 79—80° (decomp.). This methiodide rapidly decomposed with the liberation of free iodine, rendering accurate analysis impossible. Treatment of 2 : 3-dihydrothiophen with bromine yielded a yellow precipitate which immediately decomposed to a black tar with copious evolution of hydrogen bromide. The relative weight of bromine added indicated the addition of two bromine atoms per molecule.

Identification of 2 : 5-*Dihydrothiophen.—Oxidation to* 2 : 5-*dihydrothiophen* 1 : 1-*dioxide* (*β-butadiene sulphone*). A 50% excess over theory of hydrogen peroxide (42 ml.; 100-vol.) was added to 2 : 5-dihydrothiophen (12 g.) in acetic acid (75 ml.) and, after 24 hours at room temperature, the solution was refluxed for 3 hours to destroy excess of peroxide. On removal of the solvent on the water-bath at reduced pressure, a viscous oil remained which quickly solidified. Extraction with hot benzene left a small insoluble residue and addition of light petroleum to the benzene extract precipitated a white, crystalline solid (12·3 g., 75%) which recrystallised from ethanol as white nodules, m. p. 65° (Found :

C, 40·8; H, 5·2; S, 27·0. Calc. for $C_4H_4O_2S$: C, 40·7; H, 5·1; S, 27·1%). A mixed m. p. with β-butadiene sulphone which, according to Zuydewijn (*loc. cit.*), melts at 63—64° gave no depression of m. p.

3 : 4-*Dibromothiophan* 1 : 1-*dioxide*. The sulphone yielded a dibromide when treated with bromine either in refluxing carbon tetrachloride or on being kept for 12 hours in cold aqueous solution. On recrystallisation from carbon tetrachloride it formed small colourless plates, m. p. 140—141° (Found: C, 17·6; H, 2·4; S, 11·5; Br, 57·3. Calc. for $C_4H_4O_2SBr_2$: C, 17·3; H, 2·2; S, 11·55; Br, 57·5%). Zuydewijn (*loc. cit.*) obtained a dibromide from β-butadiene sulphone in a similar manner, m. p. 139—141°, to which he attributed the *trans*-structure. Staudinger and Ritzenthaler (*loc. cit.*) give m. p. 141°.

3 : 4-*Dihydroxythiophan* 1 : 1-*dioxide*. Treatment of 2 : 5-dihydrothiophen as described above, but with a 200% excess over theory of peroxide, gave only a small amount of sulphone (20%) together with the corresponding diol (80%). This remained as a residue on extraction with benzene; on recrystallisation from ethanol it formed a microcrystalline powder, m. p. 159—160° (Found: C, 31·4; H, 5·5; S, 20·9. Calc. for $C_4H_8O_4S$: C, 31·6; H, 5·3; S, 21·2%). Zuydewijn (*loc. cit.*) obtained this compound, m. p. 159—160°, from β-butadiene sulphone and peracetic acid by hydrolysing the resultant diol acetate with boiling water; he attributed to it the *trans*-structure.

3-*Bromo*-4-*hydroxythiophan* 1 : 1-*dioxide* (XVI). The insoluble oil formed by heating the crude diol under reflux with a solution of bromine in carbon tetrachloride for 2 hours solidified on storage and crystallised from ethanol as a colourless, microcrystalline powder, m. p. 190—191° (Found: C, 22·5; H, 3·3; S, 14·9; Br, 36·8. Calc. for $C_4H_7O_3SBr$: C, 22·5; H, 3·3; S, 14·2; Br, 37·15%). Van Lohuizen and Backer (*Rec. Trav. chim.*, 1949, **68**, 1137) obtained this compound, m. p. 189—190°, by the action of bromine on β-butadiene sulphone in acetic acid solution.

***Thiophan* 1 : 1-*dioxide*.** 2 : 5-Dihydrothiophen sulphone was hydrogenated at room temperature and pressure in 25% aqueous-alcoholic solution over colloidal palladium. The product was distilled under reduced pressure to give a quantitative yield of thiophan 1 : 1-dioxide, b. p. 115°/3 mm., m. p. 20·5—21·5°. The product derived from β-butadiene sulphone, by this method, melted at 20—21° (Zuydewijn, *loc. cit.*). The m. p. of a sample of dioxide, prepared by a different route, was 24·78°, and the estimated purity 96 mol. %. The calculated m. p. for zero impurity was 28·86°, thus indicating a very low cryoscopic constant.

***Identification of* 2 : 3-*Dihydrothiophen*.—*Oxidation to* 2 : 3-*dihydrothiophen* 1 : 1-*dioxide* (*α-butadiene sulphone*).** A solution of the isomer (2·2 g.) in acetic acid (20 ml.) was oxidised with hydrogen peroxide (7·5 ml.; 100-vol.) as previously described. On removal of the solvent, the crude product slowly solidified and was extracted with benzene. Dilution with light petroleum precipitated a solid which recrystallised from ethanol as colourless, crystalline granules, m. p. 49·0—49·5° (Found: C, 40·4; H, 5·3; S, 27·2. Calc. for $C_4H_6O_2S$: C, 40·7; H, 5·1; S, 27·1%). α-Butadiene sulphone, according to Zuydewijn (*loc. cit.*), melts at 48·5—49·5°.

2 : 3-*Dibromothiophan* 1 : 1-*dioxide*. On treatment of an aqueous solution of the sulphone with bromine, colourless needles of the dibromide were deposited during 2 days in the refrigerator and they were crystallised from carbon tetrachloride; they had m. p. 117—118° (Found: C, 17·4; H, 2·3; S, 11·4; Br, 57·3. Calc. for $C_4H_4O_2SBr_2$: C, 17·4; H, 2·2; S, 11·5; Br, 57·5%). The dibromide from β-butadiene sulphone had m. p. 112—115° (Zuydewijn, *loc. cit.*).

Reduction of Dihydrothiophens to Butenethiols*.—2 : 5-Dihydrothiophen** (129 g., 1·5 mols.) was reduced, in the usual way, with sodium (69 g., 3 mols.) and methanol (500 ml.) in liquid ammonia (750 ml.). During the reaction, red globules of " amalgam " appeared on the surface and slowly reacted. The products consisted of recovered dihydrothiophen (6·5 g., 5%) and butenethiol (105 g., 80%) which was immediately distilled at 15—16°/20 mm. (b. p. 101—103°/760 mm.), n_D^{20} 1·4770, leaving only a small residue (5 g.). The thiol formed a ***butenyl* 2 : 4-*dinitrophenyl sulphide as an oily precipitate which slowly solidified. After repeated crystallisation from methanol, it formed pale yellow crystals, m. p. 56—56·5° (Found: C, 47·1; H, 4·1; N, 10·9; S, 12·4. $C_{10}H_{10}O_4N_2S$ requires C, 47·2; H, 4·0; N, 11·0; S, 12·6%). A mixed m. p. with but-3-enyl 2 : 4-dinitrophenyl sulphide (m. p. 57°) gave no depression.

2 : 3-Dihydrothiophen (129 g., 1·5 mols.) was likewise reduced and yielded recovered dihydrothiophen (14 g., 10%) and butenethiol (90 g., 68%) which was immediately distilled but gave only 40% of b. p. 20—24°/30 mm. (102—106°/760 mm.), n_D^{20} 1·4690, and only 60% below 50°/30 mm. (125°/760 mm.), with a high-boiling viscous residue, n_D^{20} 1·5190. The butenyl 2 : 4-dinitrophenyl sulphide of the 40% distillate was a semi-solid oil which could not be further purified.

***Synthesis of Butenethiols*.—But-3-enethiol** and both ***cis*-** and ***trans*-but-2-enethiol** were synthesised by the same general route. The appropriate alcohol was prepared and purified before conversion into the bromide by the method of Winstein and Young (*loc. cit.*). The bromide was then converted into the thiol through the thiuronium bromide complex (*Org. Synth.*, **21**, 36). Since much confusion exists in the literature on the physical constants of certain of the intermediates, some preparative details are given.

***But-3-enol*.—Attempts** to prepare this alcohol by a modification of Juvala's method (*Ber.*, 1930, **63**, 1989), using allyl chloride and trioxymethylene, gave low yields (*ca.* 10%); better results were obtained by partial dehydration of butane-1 : 3-diol. Toluene-*p*-sulphonic acid (75 g.) and butane-1 : 3-diol (300 g.) were placed in a 1-l. flask fitted with a dropping-funnel and a long glass-packed column leading in turn to a downward condenser, an ice-cooled receiver, and finally a carbon dioxide-cooled trap. The flask was heated in an oil-bath at 200—210°, and more glycol (1000 g.) was slowly added during 7 hours with an overhead temperature of 85—90°, after which the oil-bath temperature was slowly raised to 230° for an hour. The product in the ice-cooled trap was freed from butadiene (which was collected in the second trap, stabilised, and stored) and saturated with anhydrous potassium

carbonate, and the aqueous layer run off. The oil layer was distilled, and crude but-3-enol (248 g., 23%) was obtained, b. p. 95—130°. The combined product from two runs was fractionated in a 20-plate glass-packed column to give the pure alcohol, b. p. 113·5°/760 mm., n_D^{20} 1·4200. The but-3-enyl 3 : 5-dinitrobenzoate was obtained from light petroleum as needles, m. p. 50·5°, and the phenylurethane derivative from the same solvent as needles, m. p. 27—28°.

4-Bromobutene.—The alcohol (96 g.) was mixed with pyridine (36 ml.) in a 250-ml. flask fitted with a dropping-funnel, toluene thermometer, and calcium chloride tube. Phosphorous tribromide (52 ml.) was added dropwise during 1—1·5 hours, the flask being cooled at −15° and shaken regularly. The product was distilled directly from the flask at low pressure, washed with ice-water and chilled sodium hydrogen carbonate solution, and dried. The 4-bromobutene (97 g., 35%) was a dense, colourless oil, b. p. 14°/10 mm., n_D^{20} 1·4575.

But-3-enethiol.—The bromide (97 g., 0·75 mol.) and thiourea (57 g., 0·75 mol.) were refluxed for 3 hours in ethanol (250 ml.). The solvent was removed under reduced pressure, and the thiuronium bromide complex shaken with a solution of potassium hydroxide (84 g., 1·5 mol.) in water (400 ml.). On acidification with dilute hydrochloric acid, and cooling to below 20°, the thiol separated as a green oil (20 g., 30%), which was washed with water and dried. Only 60% of the product boiled at 8—12°/18 mm. (100—104°/760 mm.), n_D^{20} 1·4690, the remainder boiling over a wide range. The but-3-enyl 2 : 4-dinitrophenyl sulphide crystallised from ethanol as yellow plates, m. p. 57°.

trans-*Crotyl Alcohol* (*But-2-enol*).—This alcohol was prepared from *trans*-crotonaldehyde (the normal commercial material), b. p. 100·5°, n_D^{20} 1·4367, and aluminium *iso*propoxide by the method of Young, Hartung, and Crossley (*J. Amer. Chem. Soc.*, 1936, **58**, 100). The crude alcohol (61%), b. p. 115—125°, was fractionated through a 20-plate column, to yield *trans*-crotyl alcohol, b. p. 121·2°/760 mm., n_D^{20} 1·4289. Its 3 : 5-dinitrobenzoate was obtained from light petroleum as pale yellow needles, m. p. 72°, and the phenylurethane derivative as fine needles, m. p. 79—80°.

trans-*Crotyl Bromide* (*1-Bromobut-2-ene*).—The alcohol (126 g.), treated by the general method previously described, yielded *trans*-crotyl bromide (190 g., 81%) which was distilled at low pressure (3 mm.) to avoid isomerisation. No attempt was made to obtain an accurate b. p. of the bromide (n_D^{20} 1·4820).

trans-*But-2-enethiol.*—Treatment of the bromide (190 g.) in the usual way yielded the *trans*-thiol (40 g., 33%), which was distilled at 15—16°/20 mm. (101—103°/760 mm.), n_D^{20} 1·4765, with negligible residue. The *trans*-crotyl 2 : 4-dinitrophenyl sulphide crystallised from methanol as fine mustard-yellow crystals, m. p. 98·5—99°.

cis-*Crotyl Alcohol.*—This was prepared from commercial 1 : 3-dichlorobut-2-ene by Hatch and Nesbitt's method (*J. Amer. Chem. Soc.*, 1950, **72**, 727). A detailed description of the synthesis is given since certain differences were found in the physical constants of the intermediates.

3-Chlorobut-2-en-1-ol.—Commercial 1 : 3-dichlorobut-2-ene (4·6 kg.) was fractionated through a 40-plate glass-packed column under reduced pressure, and the lower-boiling 1 : 3-dichlorobut-2-ene (3·78 kg.), b. p. 68—69°/100 mm., n_D^{20} 1·4722, was converted into α-3-chlorobut-2-en-1-ol by refluxing it with an equimolar amount of 10% aqueous sodium carbonate for 3 hours. The crude product (2·95 kg.) was fractionated as above and yielded the chlorobutenol (1·92 kg., 61%), b. p. 90—91°/50 mm., n_D^{20} 1·4671. The f. p. of −42·87° and the calculated f. p. for zero impurity of −42·54° indicated a purity of about 99 mol. %.

But-2-yn-1-ol.—3-Chlorobut-2-en-1-ol (1·92 kg.) was dehydrochlorinated by refluxing it for 2 hours with 20% aqueous sodium hydroxide (750 g.). Fractionation of the crude product (1·18 kg.) under reduced pressure in a 20-plate glass-packed column yielded a main fraction of but-2-yn-1-ol (482 g., 38·3%), b. p. 89·0°/100 mm., n_D^{20} 1·4542. The f. p. of −0·88° and the calculated f. p. for zero impurity of −0·59° indicated a purity of 99·0 mol. %.

cis-*Crotyl Alcohol.*—But-2-yn-1-ol (480 g.) was hydrogenated at atmospheric pressure to *cis*-crotyl alcohol, a palladium catalyst being used (Schmidt, *Ber.*, 1919, **52**, 409). Fractionation of the crude product (449 g., 93%) in a 20-plate glass-packed column at atmospheric pressure yielded *cis*-crotyl alcohol (255 g.), b. p. 123·6°/760 mm., n_D^{20} 1·4342. The alcohol melted at −90·15° and the calculated m. p. for zero impurity of −89·44° indicated a purity of 98 mol. %. The *cis*-crotyl 3 : 5-dinitrobenzoate was obtained from light petroleum as yellow needles, m. p. 55·0—55·5°, and the phenylurethane derivative as fine needles, m. p. 42·5—43·0°.

cis-*Crotyl Bromide.*—The alcohol (144 g.) was treated in the usual way, to yield *cis*-crotyl bromide (170 g., 63%) which was distilled at low pressure (2 mm.); it had n_D^{20} 1·4830.

cis-*But-2-enethiol.*—The bromide (170 g.) was converted into the thiol (42 g., 39%), which distilled at 12°/14 mm. (n_D^{20} 1·4800), with little residue. Its m. p. of −112·4° and calculated m. p. for zero impurity of −108·4° indicated a purity of the order of 90 mol. %. Spectroscopic examination indicated the presence of a maximum of 9% of the *trans*-isomer, indicating that relatively little isomerisation had occurred in conversion of the alcohol into the thiol. The *cis*-crotyl 2 : 4-dinitrophenyl sulphide crystallised from ethanol as a mustard-coloured powder, m. p. 63—65°.

Reduction of Butenethiols to Butenes and Hydrogen Sulphide.—Thiophen-derived butenethiol (88 g., 1 mol.) was dissolved in methanol (1 l.) in a 2-l. three-necked flask fitted with a sealed stirrer and a reflux condenser leading to a carbon dioxide-cooled trap. Sodium (75 g.) was added in small pieces, and the methanol was allowed to reflux freely. The low-boiling hydrocarbon product (*ca.* 25%) in the trap was shown by analysis to be entirely *n*-butenes. The residual alkaline solution was rich in sodium sulphide and, on acidification to recover unchanged thiol, yielded a substantial volume of hydrogen sulphide. The thiols obtained directly from thiophen and from 2 : 5-dihydrothiophen were successfully reduced, and the analysis of the gaseous products is given in Table II. The thiol from

2 : 3-dihydrothiophen yielded only a trace of low-boiling hydrocarbon, and, besides recovered thiol, a neutral oil (30 g., 34%) of evil odour, the bulk of which boiled above 200°/760 mm.

Our thanks are due to the Chairman of the Anglo-Iranian Oil Co. Ltd. for permission to publish these results. We also thank Mr. L. K. Maltby and Dr. H. Powell for the preparation and interpretation of spectrograms, and Mr. W. Crawford for the determination of purities.

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571. *Some Oxidation–Reduction Reactions of Hydroxylamine.*

By P. DAVIS, M. G. EVANS, and W. C. E. HIGGINSON.

Evidence is presented for the intermediate formation of the NH_2 radical in the reduction of hydroxylamine in acid, aqueous solution. This radical is able to initiate the polymerisation of vinyl monomers and to attack various aromatic substrates. A preliminary investigation of the products formed by the attack by NH_2 radicals on benzene has been made.

The overall energetics of the primary reaction between reducing agent and hydroxylamine are discussed, with reference to the observed formation of the NH_2 radical rather than the OH radical.

HYDROXYLAMINE in acid solution is reduced by strong reducing agents to ammonia and water (see, *e.g.*, Stähler, *Ber.*, 1904, **37**, 4732; Kurtenacker and Werner, *Z. anorg. Chem.*, 1927, **160**, 333) :

$$2Cr^{++} + HO{\cdot}NH_3^+ + 2H^+ \longrightarrow 2Cr^{+++} + NH_4^+ + H_2O$$

The formal similarity between this reaction and the reduction of hydrogen peroxide by ferrous ions, which under suitable conditions obeys the stoicheiometric equation :

$$2Fe^{++} + HO{\cdot}OH + 2H^+ \longrightarrow 2Fe^{+++} + H_2O + H_2O$$

has prompted an investigation of the detailed mechanism of the reactions of hydroxylamine by using methods similar to those employed in the elucidation of the mechanism of the hydrogen peroxide–ferrous reaction (Baxendale, Evans, and Park, *Trans. Faraday Soc.*, 1946, **42**, 155). In the latter case it has been established that the reaction takes place in two steps, each involving the oxidation of a ferrous ion to the ferric state, and the intermediate formation of the OH radical. This was shown by allowing substrate molecules (monomers such as methyl methacrylate) to compete with the ferrous ions for the OH radicals produced in the first stage of the reaction, thus causing a drop in the $[Fe^{++}]/[H_2O_2]$ consumption fraction from 2 in the absence of substrate, to 1 in high substrate concentrations.

In the reduction of hydroxylamine in the presence of substrate (X), there are two extreme possibilities, *viz.* :

1 (*a*) $M^{n+} + HO{\cdot}NH_3^+ \longrightarrow M^{(n+1)+} + (H^+ + NH_2^-) + OH^-$
(*b*) $M^{n+} + OH \longrightarrow M^{(n+1)+} + OH^-$
(*c*) $OH + X \longrightarrow X{\cdot}OH$

2 (*a*) $M^{n+} + HO{\cdot}NH_3^+ \longrightarrow M^{(n+1)+} + NH_2 + (OH^- + H^+)$
(*b*) $M^{n+} + NH_2 \longrightarrow M^{(n+1)+} + NH_2^-$
(*c*) $X + NH_2 \longrightarrow XNH_2$

The overall reaction may involve the intermediate formation of OH radicals or of NH_2 radicals or possibly both. The main aim of this investigation has been the attempt to decide whether the NH_2 radical, which does not appear to have been reported previously as an intermediate in reactions in aqueous solution, is produced in this system.

EXPERIMENTAL.

Cylinder nitrogen was partially freed from oxygen by passage through columns containing a solution of sodium dithionite, sodium hydroxide, and sodium anthraquinone-β-sulphonate. The gas was

finally purified by passage through a tower of finely divided copper on kieselguhr at 220° (Meyer and Ronge, *Angew. Chem.*, 1939, **52**, 637). This oxygen-free gas was used in all cases where de-aeration of solutions was necessary.

Hydroxylamine hydrochloride was of " AnalaR " quality. Hydroxylamine sulphate was a B.D.H. product and was recrystallised once from water. Titanium(III) sulphate and titanium(III) chloride solutions were obtained from Messrs. Peter Spence, and were found to contain 0·070 and 0·018 mole of the corresponding ferrous salt, respectively, per mole of titanous salt. Iron-free titanium(III) chloride was prepared by the electrolytic reduction of a solution of pure titanium(IV) chloride in M-hydrochloric acid, at a lead cathode. In the experiments described, however, the presence of small quantities of ferrous ion proved to be unimportant.

Solutions of chromium(II), vanadium(II), and molybdenum(III) sulphates* were prepared by the zinc-amalgam reduction of solutions of chromium(III) sulphate, vanadium(IV) sulphate, and molybdic acid (all " AnalaR "), respectively, in N-sulphuric acid.

Methyl methacrylate was obtained from Imperial Chemical Industries Limited, and was freed from stabilisers with potassium hydroxide solution followed by vacuum distillation under nitrogen. Acrylonitrile was obtained from L. Light & Co. and was purified by fractional distillation under nitrogen. Other reagents were of B.D.H. " AnalaR " quality.

In the preliminary experiments, measured quantities of solutions of the reducing agent were added to solutions of hydroxylamine sulphate, previously de-aerated by passage of oxygen-free nitrogen, in the presence of methyl methacrylate or of acrylonitrile. The solutions were kept under an atmosphere of nitrogen. The concentrations of reducing agent and of hydroxylamine sulphate were of the order 10^{-3}M.—2×10^{-2}M. and the sulphuric acid concentration 10^{-2}—2N. Monomer concentrations were 0·05M. in the case of methyl methacrylate and 1M. in the case of acrylonitrile.

Under these conditions titanium(III) was oxidised rapidly, and almost immediate formation of visible polymer occurred. In similarly dilute acid solutions chromium(II), vanadium(II), and molybdenum(III) were slowly oxidised, and visible polymer appeared only after about ten minutes. With iron(II) (in 10^{-2}N-sulphuric acid) several days elapsed before the appearance of polymer; after a month, a considerable amount of polymer had been formed, though tests on the solution showed no iron(III). It is, however, known that in acid solution iron(III) is reduced fairly rapidly to iron(II) by hydroxylamine (Mitchell, *J.*, 1926, 336). The use of iron(II) in the presence of acetate ion and of fluoride ion at pH $\simeq$ 5 caused a considerable decrease in the time of appearance of polymer, but even so the reaction appeared to be very slow. Ferrocyanide in acid, neutral, and alkaline solution gave no trace of polymer after several weeks. In all the above cases parallel experiments, carried out in the absence of reducing agent or of hydroxylamine, showed no evidence of polymer formation.

The production of polymer is strong evidence for the formation, as reaction intermediates, of radicals able to attack the double bond of a vinyl monomer, and hence is evidence in favour of the two-stage nature of the overall reaction.

In more detailed experiments on the stoicheiometry of the reaction in the presence of substrates, titanium(III) was used as the reducing ion, as in this case comparatively short reaction times could be achieved. Moreover the reaction between titanium(III) and hydroxylamine is known to be stoicheiometric under the appropriate conditions, and can be used for the quantitative determination of hydroxylamine (Stähler, *loc. cit.*; Bray, Simpson, and MacKenzie, *J. Amer. Chem. Soc.*, 1919, **41**, 1363).

These experiments were carried out by adding about a 20% excess of standard titanium(III) chloride solution to previously de-aerated solutions of hydroxylamine hydrochloride and methyl methacrylate. The mixture was well stirred in an atmosphere of nitrogen for 30 minutes, and then the excess of titanium(III) chloride was titrated against standard cerium(IV) sulphate solution, *N*-phenylanthranilic acid being used as indicator. The mixture was then made alkaline with sodium hydroxide solution, and ammonia determined by the Kjeldahl method. Blank experiments were done in the absence of hydroxylamine; the blank correction was reproducible and equivalent to 2% of the ammonia produced in the absence of monomer. The time of addition of the titanium(III) chloride solution from a microburette was in all cases approximately 90 seconds; check experiments in which the time of addition was varied between 30 seconds and 8 minutes showed that within this range the rate of addition had no detectable effect on the stoicheiometry. Under the conditions of the experiments the half life of the reaction was of the order of 2 minutes, so that 30 minutes was an ample allowance for complete reaction. The experiments were done mainly at room temperature (20° $\pm$ 1°); a few experiments at 10° and 30° gave results identical within the experimental error.

Fig. 1 shows the dependence of the consumption fraction $[Ti^{3+}]/[HO{\cdot}NH_3^+]$ on monomer concentration; Fig. 2 shows the dependence of $[NH_3]_{evolved}/[HO{\cdot}NH_3^+]_{consumed}$ on monomer concentration, in the same set of experiments; while Fig. 3 shows $[Ti^{3+}]/[HO{\cdot}NH_3^+]$ plotted against $[NH_3]_{evolved}/[HO{\cdot}NH_3^+]_{consumed}$. The concentration of methyl methacrylate varied from zero to a 2M-emulsion; $[HO{\cdot}NH_3^+] = 5 \times 10^{-3}$M., [HCl] = 0·6N.

Reference to equations 1*a*, *b*, and *c* and 2*a*, *b*, and *c* shows that only if the primary reaction is 2*a* exclusively can the experimental finding (Fig. 3)

$$[Ti^{3+}]_{consumed}/[HO{\cdot}NH_3^+]_{consumed} = 1 + \{[NH_3]_{consumed}/[HO{\cdot}NH_3^+]_{consumed}\}$$

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* The possible complexes formed by these ions in solution have not been specified since we are dealing only with the overall stoicheiometry and not with the detailed mechanism.

be satisfied. The other extreme, involving the exclusive production of the OH radical, would lead to a constant $[NH_2]_{evolved}/[HO{\cdot}NH_3^+]_{consumed}$ of unity, independently of value of $[Ti^{3+}]_{consumed}/[HO{\cdot}NH_3^+]_{consumed}$. It thus appears that the NH_2 radical is an intermediate in the reduction of hydroxylamine, and that it is an effective initiator of polymerisation. The weight-average molecular weight of the polymer as determined by viscosity experiments varied between 40,000 and 300,000. Determination of the nitrogen content of the polymers was not attempted.

FIG. 1.

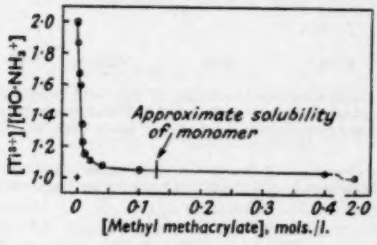


FIG. 2.

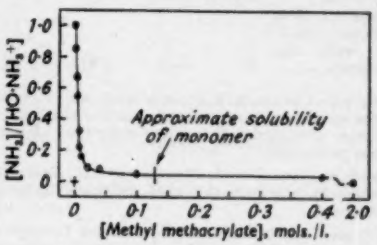


FIG. 3.

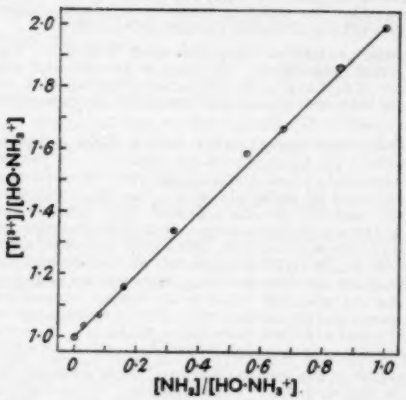
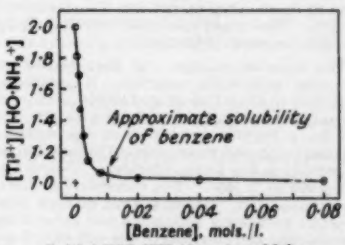
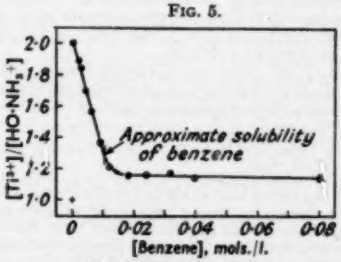


FIG. 4.



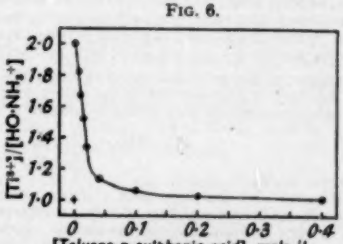
Initial $[HO{\cdot}NH_3^+] = 4 \times 10^{-3}$M.

FIG. 5.



Initial $[HO{\cdot}NH_3^+] = 10^{-3}$M.

FIG. 6.



Initial $[HO{\cdot}NH_3^+] = 2 \times 10^{-3}$M.

Substrates other than methyl methacrylate were also used, and Figs. 4 and 5 show the consumption fraction $[Ti^{3+}]/[HO{\cdot}NH_3^+]$ plotted against benzene concentration. In Fig. 4 the acid was 0·6N-hydrochloric acid; $[HO{\cdot}NH_3^+] = 4 \times 10^{-3}$M.; in Fig. 5 titanium(III) sulphate was used, the acid was 0·4N-sulphuric acid and $[HO{\cdot}NH_3^+] = 10^{-3}$M. Fig. 6 shows the consumption fraction plotted against toluene-*p*-sulphonic acid concentration. Here the total acid strength was maintained at 0·4N. in each experiment by the addition of the appropriate amount of sulphuric acid; $[HO{\cdot}NH_3^+]$ was 0·02M.

The table shows the consumption fraction for 0·02M-hydroxylamine in 0·5N-sulphuric acid in the presence of 0·1M-solutions of various substrates.

Substrate.		Pyridinium ion.	Toluene (emulsion).	Benzene (emulsion).	Benzoic acid (heterogeneous).	Naphthalene-2-sulphonic acid.	Toluene-*p*-sulphonic acid.	Benzenesulphonic acid.
Consumption fraction $[Ti^{3+}]/[HO{\cdot}NH_3^+]$ ...	2·0	1·98	1·33	1·24	1·17	1·12	1·07	1·04
Fraction of NH_2 radicals reacting with the substrate	0	0·02	0·67	0·76	0·83	0·88	0·93	0·96

The use of aromatic sulphonic acids may thus prove advantageous in studies of this kind, where the use of monomer is inconvenient because of the high concentrations often needed and the heavy precipitate of polymer produced. It is noteworthy that apparently the pyridinium ion does not react with the NH_2 radicals produced.

Products Formed by the Reaction of NH_2 *Radicals and Benzene.*—A few preliminary experiments have been made to determine the products formed by the titanium(III)–hydroxylamine reaction in the presence of benzene.

Nitrogen was bubbled for 30 minutes through sulphuric acid (500 ml.; N.) and benzene (100 ml.) contained in a 2-litre flask. De-aerated, approximately M-solutions of titanium(III) sulphate and hydroxylamine sulphate were run in simultaneously with vigorous stirring; about 50—100 ml. of each solution were used, and the time of addition was 30—60 minutes. The addition was so controlled that the hydroxylamine was always in slight excess until the end of the addition, when the titanium solution was added in slight excess, which was then removed by addition of a small amount of ferric iron.

The benzene layer was then separated, and the solution extracted twice with ether (250 ml.). The benzene, and the ether extracts, were dried (Na_2SO_4) and evaporated. No trace of any product was found in these extracts, nor was the characteristic odour of diphenyl noticeable after evaporation of the solvents. Test experiments showed that diphenyl can be recovered almost quantitatively on evaporation of a dilute solution in benzene.

The aqueous mixture was then cooled in an ice-bath and made alkaline with a slight excess of potassium hydroxide solution. A gelatinous precipitate of hydrated titania resulted. It proved impossible to filter this off and so the mixture was extracted with ether (500 ml.), and the ethereal extract was extracted with hydrochloric acid (20 ml.; 2N.) followed by water (10 ml.). The ether was then used for a further extraction of the aqueous mixture, and the process repeated eight times. The combined acid and water extract (about 250 ml.) should contain any amines produced in the reaction, as the corresponding hydrochlorides. Evaporation of part of the solution gave, on cooling, diphenyl, m. p. and mixed m. p. 69°. The remainder of the solution was made alkaline, extracted with ether, and the ether evaporated. About 0·5 ml. of dark brown oil remained, and this gave a positive test for nitrogen. Alcoholic potassium hydroxide and chloroform gave the characteristic odour of an organic *iso*cyanide; diazotisation and coupling of the salt with β-naphthol gave a red precipitate which slowly decomposed to a brown oil; attempts to prepare a benzoyl derivative and a picrate gave tarry products. It seems probable, therefore, that the brown oil contained an aromatic amine, though no aniline could be detected.

Qualitative experiments showed that if, after separation of the benzene layer and ether extracts, the acid aqueous reaction mixture was boiled diphenyl was formed in fairly large amounts. Accordingly a quantitative experiment was done in which the acid reaction mixture, obtained as previously described, was refluxed for 6 hours and the diphenyl formed then steam-distilled. The total diphenyl obtained was approximately 0·12 g.-mol. (*i.e.*, equivalent to 0·24 g.-radical of NH_2) while the amounts of hydroxylamine and titanium(III) used in the experiment (consumption fraction $[Ti^{3+}]/[HO{\cdot}NH_3^+] = 1{\cdot}2$) showed that approximately 2·4 g.-radicals of NH_2 had attacked the benzene substrate.

As no trace of diphenyl was found in either the benzene layer or the ethereal extracts of the cold acid reaction mixture, it seems probable that the reaction between an NH_2 radical and a benzene molecule in aqueous solution does not lead to the formation of phenyl radicals and ammonia, *viz.*,

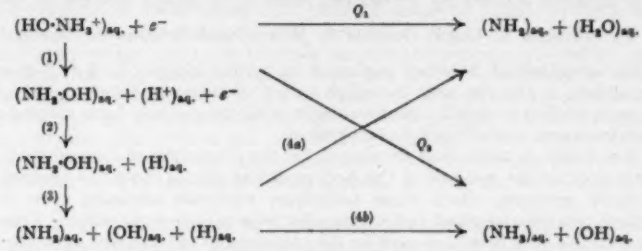
$$NH_2 + H{\cdot}C_6H_5 \longrightarrow NH_3 + C_6H_5{\cdot}$$
$$(2C_6H_5{\cdot} \longrightarrow C_6H_5{\cdot}C_6H_5)$$

Consistently with the experimental observations, it is suggested that the primary product of attack of NH_2 radicals on benzene is the addition compound $C_6H_6{\cdot}NH_2$, and that a proportion of these radicals dimerise to give a di(amino*cyclo*hexadienyl); such compounds do not appear to have been recorded in the literature. It seems likely, however, that boiling in acid solution could cause loss of ammonia with the formation of diphenyl. As the total diphenyl production was only of the order of 10% of the amount to be expected if all the NH_2 radicals which reacted with the benzene had led to diphenyl formation, a major proportion of $C_6H_6{\cdot}NH_2$ radicals, rather than dimerising, must undergo other reactions, possibly addition of NH_2 or even oxidation by the NH_2 radical.

Discussion of the Energetics of the Primary Reaction.

The experimental results show that the first step in the reduction of hydroxylamine in acid solution results almost completely, possibly exclusively, in the formation of NH_2 radicals; a

consideration of the relevant energy proves of interest. From the following cycles, the influence of these factors on the overall energy change of reaction can be seen:



It thus appears that the difference of heats of reactions involving the formation of NH_2 or of OH radicals, *i.e.* $(Q_1 - Q_2)$, is determined solely by the terms:

$$D^{aq.}_{HO\text{-}H} - D^{aq.}_{NH_2\text{-}H} = D^{gas}_{HO\text{-}H} + (S^{aq.}_{H_2O} - S^{aq.}_{OH}) - D^{gas}_{NH_2\text{-}H} - (S^{aq.}_{NH_2} - S^{aq.}_{NH_2})$$

where D's are bond dissociation energies and S's are solution energies.

We suggest that the second and the fourth term in the above equation are small and roughly equal, *i.e.*,

$$(S^{aq.}_{H_2O} - S^{aq.}_{OH}) \sim (S^{aq.}_{NH_2} - S^{aq.}_{NH_2})$$

There are no direct evaluations of the heats of solution of the free radicals OH and NH_2, but we can obtain an idea of the magnitude of these terms from considerations of the heats of solution of hydrogen peroxide, water, hydrazine, and ammonia:

Molecule.	H_2O_2.	H_2O.	N_2H_4.	NH_3.
Heat of solution in water, kcals./mole	12	10·5	14	8·5

The heat of dissociation of hydrogen peroxide into two OH radicals in water does not differ appreciably from the dissociation heat in the gas phase, suggesting that $S^{aq.}_{H_2O_2} = 2S^{aq.}_{OH}$. Such considerations support the assumption made above, and hence we suggest that

$$Q_1 - Q_2 = D^{gas}_{HO\text{-}H} - D^{gas}_{NH_2\text{-}H}$$

The recent values of 118 and of 104 kcals./mole for the bond dissociation energy of HO–H (Dwyers and Oldenburg, *J. Chem. Phys.*, 1944, **12**, 351) and of NH_2–H (Szwarc, *J. Chem. Phys.*, 1949, **17**, 505), respectively, being used, the overall heat of the primary reaction is calculated to be at least 12·5 kcals. more exothermic in the case where NH_2 radicals are produced than with the alternative OH-radical production, and this difference can be ascribed mainly to the greater heat of formation of the H–OH bond compared with the NH_2–H bond. The qualitative parallelism which exists for simple primary steps between the rates and the overall energy changes of similar reactions may be expected to apply in this case, and thus the experimental finding of exclusive NH_2-radical production may be understood.

It is important to notice that these conclusions hold whether $NH_2{\cdot}OH{\cdot}H^+$ or $NH_2{\cdot}OH$ is the reacting species, as up to 4 (*a*, *b*) the steps in the energy cycle are identical.

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572. *Monoalkyl Hexoses: Improved Procedures for the Preparation of 1- and 3-Methyl Ethers of Fructose, and of 3-Alkyl Ethers of Glucose.*

By William L. Glen, Gordon S. Myers, and Gordon A. Grant.

The synthesis of 3-methyl D-glucose by way of glucose, 1 : 2-5 : 6-di*iso*propylidene D-glucose, and 3-methyl 1 : 2-5 : 6-di*iso*propylidene D-glucose has been studied in detail; improvements at all three stages have enabled a much increased overall yield to be obtained.

New methods have been developed for the alkylation of *iso*propylidene sugars and for the removal of the *iso*propylidene groups from the resultant alkylated products. Both these techniques represent advances over the methods hitherto described and are thought to be of wide application. These new methods have now been used for the preparations of three new monoalkyl glucoses and for the preparation of 3-methyl D-fructose.

Convenient procedures for the preparation of 1- and 3-methyl D-fructose have been developed, using sucrose or invert sugar as initial starting material.

Studies of its metabolism have demonstrated that 3-methyl glucose possesses interesting properties (Campbell and Danson, *Biochem. J.*, 1948, **43**, 426; Campbell, *ibid.*, 1949, **44**, 41; *Nature*, 1949, **164**, 365) and prompted an investigation of the synthesis of 3-methyl glucose and other 3-alkyl derivatives of glucose. It was thought that the non-glucosidic monomethyl derivatives of fructose might also be of pharmacological interest and accordingly 1- and 3-methyl D-fructose were selected for initial studies and synthesized by the procedures described in this paper.

The methods hitherto described for the preparation of 3-methyl D-glucose by way of the intermediate compounds 1 : 2-5 : 6-di*iso*propylidene and 3-methyl 1 : 2-5 : 6-di*iso*propylidene D-glucose cannot be considered wholly satisfactory in view of the low overall yields, and, accordingly, each of the three steps of the synthesis has now been examined in detail. The first stage has been considerably improved by the use of condensing agents which minimize side reactions, but it is at the two subsequent stages (methylation of di*iso*propylidene glucose and later removal of the *iso*propylidene groups) that improvement has been most marked. As a result of these studies a convenient laboratory method for the preparation of 3-methyl glucose has been developed and the overall yield has been raised to 60—65%.

Two new methods have been developed for the methylation of di*iso*propylidene glucose. Both give almost theoretical yields of 3-methyl di*iso*propylidene glucose and were designed with the economic utilization of the methylating agent as a primary objective. In the first method, a moderate excess (50%) of methyl sulphate is employed in presence of solid, pulverized sodium hydroxide and acetone; in the second method methyl chloride is used under pressure and in presence of acetone and solid sodium hydroxide. Both these procedures deviate considerably from established techniques employing alkylating agents such as methyl iodide and silver oxide (Irvine and Hynd, *J.*, 1909, **95**, 1220), an alkyl halide and metallic sodium (Freudenberg and Hixon, *Ber.*, 1923, **56**, 2119) or methyl sulphate and potassium hydroxide (Schmidt and Simon, *J. pr. Chem.*, 1939, **152**, 194).

The *iso*propylidene groups in 3-methyl di*iso*propylidene glucose are labile and readily removed by the action of dilute mineral acids, but despite this the methods hitherto described for the hydrolysis employ relatively large quantities of acid which must be eliminated from the final hydrolysate by, *e.g.*, barium carbonate (Loder and Lewis, *J. Amer. Chem. Soc.*, 1932, **54**, 1045), silver carbonate (Irvine *et al.*, *J.*, 1913, **569**; 1914, 1390), or lead acetate (Schmidt and Simon, *J. pr. Chem.*, 1939, **152**, 194), and the methods are protracted. Two laboratory hydrolytic procedures have now been developed which avoid large quantities of acid. In the first an aqueous suspension of an acid-form ion-exchange resin is used as hydrolysing agent; in the second, water acidified to pH 2—3 is employed. Both avoid the usual tedious purifications and crystalline 3-methyl glucose is isolated from the hydrolysate, simply by concentration, in yields of at least 85%.

It is probable that these methods are of general application for the hydrolysis of sugar derivatives possessing labile *iso*propylidene groups. They have been found effective in the preparation of three new alkylated glucoses, namely, 3-ethyl, 3-*n*-propyl, and 3-*n*-butyl D-glucose.

The methods developed for the synthesis of 3-methyl glucose gave equally satisfactory results when applied to the preparation of 3- and 1-methyl fructose. Alkylations of " α "- and " β "-di*iso*propylidene fructose (respectively the 1 : 2-4 : 5- and 2 : 3-4 : 5-isomers; Wolfram, Shilling, and Blinkley, *J. Amer. Chem. Soc.*, 1950, **72**, 4544), by methyl sulphate in presence of solid sodium hydroxide, gave excellent yields (upwards of 90%) of 3- and 1-methyl di*iso*propylidene fructose and were superior to the methods described by Irvine and Hynd (*loc. cit.*), Freudenberg and Hixon (*loc. cit.*), and Ohle (*Ber.*, 1925, **58**, 2577). Hydrolysis of 3-methyl di*iso*propylidene fructose was effected smoothly by either of the hydrolytic procedures described for 3-methyl glucose, giving pure 3-methyl fructose in 85—90% yield without recourse to complex isolation procedures. Removal of the *iso*propylidene groups from 1-methyl di*iso*propylidene fructose necessitates relatively vigorous conditions but can be effected by 0·1N-sulphuric acid at 100°; the excess of acid can be eliminated from the hydrolysate by a suitable ion-exchange resin.

The intermediate " β "-di*iso*propylidene fructose required for these studies was prepared in 70—80% yield from sucrose and acetone by a process parallel to that described for the preparation of di*iso*propylidene glucose, a mixture of zinc chloride and phosphoric acid being used to effect fission of sucrose and introduction of the *iso*propylidene residues. The product was freed from concomitant di*iso*propylidene glucose by the methods outlined by Bell (*J.*, 1947, 1461).

Although " α "-di*iso*propylidene fructose can be prepared satisfactorily from fructose, a less expensive starting material seemed desirable and attempts were, therefore, made to develop processes starting from sucrose or invert sugar. The actions of condensing agents on glucose–acetone and fructose–acetone mixtures have been recorded by various workers but no attempt has been made to correlate the results and apply them to the preparation of the " α "-derivative. By using invert sugar and acetone as starting materials, and zinc chloride as condensing agent, it has been possible to prepare " α "-di*iso*propylidene fructose in satisfactory yields and of a quality which permits procedure to the next stage of the synthesis of 3-methyl fructose (methylation) without further purification. The preparation is based on the fact that under the conditions of the reaction, fructose is converted into " α "-di*iso*propylidene fructose, whereas the concomitant glucose forms little or no di*iso*propylidene derivative and can be removed from the product by partitioning between chloroform and water. An attempt to use sucrose as starting material gave less satisfactory results, but it has been possible to demonstrate that fission of sucrose and production of " α "-di*iso*propylidene fructose can be effected by using 0·3% sulphuric acid in presence of acetone. The series of reactions described above render 3-methyl fructose a readily available and comparatively inexpensive compound.

Our studies indicated that a mixture of approximately equal quantities of 3-methyl glucose and 1-methyl fructose might be of pharmacological interest. Accordingly such a mixture was prepared from sucrose by the four step process. In a similar manner mixtures of the corresponding ethylated and propylated hexoses were obtained.

Experimental.

Evaporation of solvents, when not otherwise stated, was conducted below 70° and under reduced pressure.

1 : 2-5 : 6-*Diisopropylidene Glucose from Glucose.*—To an efficiently stirred suspension of anhydrous glucose (150 g.) in acetone (1 l.) anhydrous pulverized zinc chloride (120 g.) was added, followed by 85% phosphoric acid (7·5 g.). This mixture was stirred at room temperature for 30 hours and the undissolved glucose (61·8 g.) was collected and washed with a little acetone. The filtrate and washings were cooled and made slightly alkaline with sodium hydroxide solution (85 g. of sodium hydroxide in 85 ml. of water), and the insoluble inorganic material removed by filtration and washed with acetone. The almost colourless filtrate and washings were concentrated and the residue was diluted with water (150 ml.) and extracted thrice with chloroform (3 × 150 ml.). The combined chloroform extracts were washed with a little water and concentrated to give a white crystalline residue of crude di*iso*propylidene glucose (115·4 g., 91% yield based on the glucose consumed), m. p. 95—101°. One crystallization from 1 : 2 chloroform–hexane raised the m. p. to 105—109°, but the crude product is satisfactory for the next step.

3-*Methyl* 1 : 2-5 : 6-*Diisopropylidene Glucose.*—(a) *By use of methyl sulphate.* A mixture of di*iso*propylidene glucose (78 g.), acetone (75 ml.), and pulverized sodium hydroxide (32 g.) was warmed under reflux to 45° with stirring and methyl sulphate (42·6 ml.) was added dropwise at this temperature during 90 minutes. The methylation was completed by warming the mixture to 50° for an additional 90 minutes and finally to 55—60° for 3 hours. The reaction mixture was diluted with water and the product extracted with chloroform (3 × 150 ml.). The chloroform extracts were washed with water and concentrated (finally at 1—3 mm. and on a steam-bath—in order to remove acetone polymers). The residual light amber-coloured crude liquid 3-methyl di*iso*propylidene glucose (83 g.) was suitable for hydrolysis to 3-methyl glucose without further purification.

(b) *By use of methyl chloride and sodium hydroxide.* A stainless-steel, rocking-type autoclave was cooled below −40° and charged with di*iso*propylidene glucose (52 g.), pulverized sodium hydroxide (24

g.), acetone (50 ml.), and liquid methyl chloride (26 ml.). The autoclave was then sealed and warmed with agitation to 145—150° for 8 hours. The mixture was then cooled and diluted with water and the 3-methyl di*iso*propylidene glucose (55 g.) isolated as in (a).

Hydrolysis of 3-*Methyl Diisopropylidene Glucose to* 3-*Methyl Glucose.*—(a) *With water at* pH 2·6. The crude 3-methyl di*iso*propylidene glucose obtained as above (*a*) (83 g.) was refluxed for 6 hours with water (150 ml.), adjusted to pH 2·6 with sulphuric acid. The warm amber-coloured hydrolysate was decolorized with charcoal ("Norit," 4 g.) and concentrated to a syrup from which final traces of water were removed by repeated evaporation with ethanol. The partly crystalline residue was warmed with methanol (45 ml.) and kept overnight at room temperature. The white crystalline 3-methyl glucose which separated (43 g.) was collected and washed with a little methanol; it had m. p. 166—168°. The mother-liquors gave a further quantity (7·1 g.; m. p. 164—167°). The total yield was 86%, based on the crude 3-methyl di*iso*propylidene glucose used.

(b) *By use of an acid ion-exchange resin.* A suspension of 3-methyl di*iso*propylidene glucose (133·8 g.) and ion-exchange resin (25 g. "IR-120," Rohm and Haas Co., Philadelphia, which was activated to the acid form by washing with 10% aqueous hydrochloric acid and then rinsing with distilled water), in water (135 ml.), was stirred at 100° for 4 hours. The resin was removed by filtration, the filtrate decolorized with charcoal, and the crystalline 3-methyl glucose isolated in good yield as in (a).

3-*Ethyl* 1 : 2·5 : 6-*Diisopropylidene Glucose.* A mixture of di*iso*propylidene glucose (78 g.), pulverized sodium hydroxide (32 g.), and acetone (75 ml.) was warmed with stirring to 45° and treated with ethyl sulphate (61 ml.) as described for the methyl analogue. The yield of crude amber-coloured liquid 3-ethyl di*iso*propylidene glucose (96 g.) was almost theoretical.

3-*Ethyl Glucose.*—Crude 3-ethyl di*iso*propylidene glucose (96 g.) was refluxed for 6 hours with 3 parts of water adjusted to pH 2·6 with sulphuric acid. The warm hydrolysate so obtained was decolorized with charcoal and concentrated, final traces of water being removed by evaporation with alcohol as described for 3-methyl glucose. The semi-solid residue was crystallized by warming it with acetone (150 ml.) and setting the mixture aside overnight at room temperature. The white, crystalline 3-*ethyl* D-*glucose* (51 g., 82%; m. p. 132—135°) was recrystallized several times from methanol–ether and then had m. p. 137—138° and $[\alpha]_D^{25}$ + 26·1° (5 minutes) ⟶ + 55·2° (constant after 24 hours) (*c*, 2 in water) (Found: C, 46·5; H, 7·9; OEt, 21·0. $C_8H_{14}O_6$ requires C, 46·2; H, 7·7; OEt, 21·6%).

3-n-*Propyl* 1 : 2·5 : 6-*Diisopropylidene Glucose.*—Di*iso*propylidene glucose (52 g.), acetone (50 ml.), *n*-propyl bromide (74 g.), and pulverized sodium hydroxide (32 g.) were warmed in an autoclave, with agitation, at 150° for 9 hours. The contents were cooled and extracted with chloroform, and the combined chloroform extracts washed with water and concentrated to a light amber-coloured liquid residue of crude 3-*n*-propyl di*iso*propylidene glucose (65 g.) which probably contained some high-boiling acetone polymers but was suitable for hydrolysis to 3-propyl glucose without further purification.

3-n-*Propyl Glucose.*—Crude 3-*n*-propyl di*iso*propylidene glucose obtained as above (65 g.) was boiled for 8 hours with 3 parts of water adjusted to pH 2·1 with sulphuric acid. The hydrolysate was then extracted with chloroform (2 × 75 ml.) to remove dark impurities, and the chloroform extracts were washed with a little water. The aqueous hydrolysate and water washings were combined, warmed, decolorized with charcoal (3 g.), and then concentrated: the final traces of water were removed by addition of alcohol to the residue and subsequently evaporation under reduced pressure in the usual manner. The solid crystalline residue of 3-n-*propyl* D-*glucose* was collected and washed with a little ether (38·3 g., 86% based on the di*iso*propylidene glucose used in the previous stage; m. p. 129—131°). Two recrystallizations from methanol–ether raised the m. p. to 130—131°; $[\alpha]_D^{25}$ was +29·5° (5 minutes) ⟶ +62·3° (constant after several hours) (*c*, 2 in water) (Found: C, 49·1; H, 8·25; OPr, 27·4. $C_9H_{18}O_6$ requires C, 48·6; H, 8·15; OPr, 26·8%).

3-n-*Butyl* 1 : 2·5 : 6-*Diisopropylidene Glucose.*—*n*-Butyl bromide (82·2 g.), di*iso*propylidene glucose (52 g.), pulverized sodium hydroxide (36 g.), and acetone (50 ml.) were warmed together in an autoclave at 150° for 9 hours. The crude 3-n-*butyl diisopropylidene* D-*glucose* (isolated as described for the 3-*n*-propyl analogue) was distilled and the fraction of b. p. 120—123°/1 mm. was collected (55·2 g., 87%; $[\alpha]_D^{25}$ + 70·5° (*c*, 2 in chloroform); n_D^{27} 1·4513) (Found: C, 62·3; H, 8·9. $C_{14}H_{24}O_6$ requires C, 60·7; H, 8·9%).

3-n-*Butyl Glucose.*—The foregoing distilled compound (42 g.) was refluxed for 8 hours with 3 parts of water adjusted to pH 2·1 with sulphuric acid, and the 3-n-*butyl* D-*glucose* was isolated from the hydrolysate as described for 3-*n*-propyl glucose. The crude product (29·7 g., 98%; m. p. 130—134°), crystallized twice from methanol–ether, had m. p. 137—139° and $[\alpha]_D^{25}$ +23·7° (5 minutes) ⟶ +52·1° (constant after several hours) (*c*, 2 in water) (Found: C, 51·2; H, 8·6. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·55%).

"*β*"-*Diisopropylidene Fructose.*—(a) *From fructose.* A cold solution of phosphoric oxide (1·5 g.) in 85% phosphoric acid (3 g.) was added to a mixture of fructose (27 g.), anhydrous zinc chloride (36 g.), and acetone (180 ml.), and the resulting mixture was efficiently agitated at room temperature for 26 hours. The contents were then made alkaline with sodium hydroxide (35 g. of sodium hydroxide in 35 ml. of water), and the inorganic precipitate was filtered off and washed with acetone. The filtrate and washings were concentrated and the residue was diluted with water and extracted with chloroform. Evaporation of the chloroform gave crude *β*-di*iso*propylidene fructose (32·5 g.; m. p. 78—85°) which was purified by being stirred at room temperature for 8 hours with 0·1N-sulphuric acid (to hydrolyse any "*α*"-di*iso*propylidene fructose; Bell, *loc. cit.*). The product (24·4 g., 63%; m. p. 94·5—95°) was extracted from the hydrolysate with chloroform.

(b) *From sucrose.* To a well-stirred mixture of sucrose (150 g.) and acetone (1 l.) was added anhydrous zinc chloride (120 g.), followed by a cold solution of phosphoric oxide (10 g.) in 85% phosphoric acid (20 g.). The mixture, which warmed spontaneously to 40°, was stirred at room temperature for 24 hours

by which time all the sugar had dissolved. A solution of sodium hydroxide (120 g. of sodium hydroxide in 120 ml. of water) was added dropwise with cooling, and the precipitated inorganic salts were collected and washed with acetone. The filtrate and washings were concentrated and the residue was diluted with water (800 ml.) and extracted with chloroform (4 × 200 ml.). The chloroform extracts were washed with water and concentrated. The residue so obtained was stirred for 6 hours with 0·1N-sulphuric acid (500 ml.) to hydrolyse the di*iso*propylidene glucose (and " α "-di*iso*propylidene fructose, if present). Extraction of the hydrolysate with chloroform in the usual manner gave " β "-di*iso*propylidene fructose (84 g., 74%; m. p. 90—93°). A sample twice crystallized from hexane melted at 94·5—95°.

1-*Methyl Diisopropylidene Fructose from* " β "-*Diisopropylidene Fructose.*—(a) *By use of methyl sulphate.* A mixture of " β "-di*iso*propylidene fructose (200 g.), acetone (200 ml.), and pulverized sodium hydroxide (135 g.) was treated at 45°, with stirring, with methyl sulphate (146 ml. added dropwise during 90 minutes). The mixture was then warmed to 50° for 1 hour and finally to 55—60° for 3 hours. The suspension was diluted with water and extracted with chloroform (4 × 200 ml.), and the chloroform extracts were washed with water and evaporated [1—2 mm., 100° (bath); removal of acetone polymers]. The residue of crude 1-methyl di*iso*propylidene fructose (215 g.) was crystallized at −40° from 3 : 2 methanol–water (475 ml.) to give a white crystalline product (182 g.; m. p. 48—48·5°). A second crop weighed 14 g. and had m. p. 46—47° (total yield, 93%).

(b) *By use of methyl iodide.* " β "-Di*iso*propylidene fructose (100 g.) in dry benzene (500 ml.) was added to metallic sodium (25 g.; powdered under toluene) and left for 24 hours at room temperature. The benzene solution was decanted from unchanged sodium, then concentrated, and the residue treated with methyl iodide (110 ml.). The mixture was kept, with occasional shaking, for 4 days at room temperature and finally diluted with ether, filtered to remove sodium iodide, and concentrated. The residue was crystallized from hexane and gave 96·5 g. (92%) of material, m. p. 45—47°.

1-*Methyl Fructose.*—A suspension of 1-methyl di*iso*propylidene fructose (411 g.) in three parts of 0·1N-sulphuric acid was warmed with stirring to 95—100° for 7 hours, by which time the sugar had dissolved and hydrolysis was complete. The warm, amber-coloured solution was decolorized with charcoal (12 g.; " Norit "), concentrated to 600 ml. and re-treated with charcoal. The sulphuric acid was then removed from the hydrolysate by stirring with either barium carbonate (40 g.) or an ion-exchange resin (Amberlite IRA-400, basic form; Rohm and Haas Co., Philadelphia). The final pH was adjusted to 5—5·5 since at this pH discoloration was minimized. The sugar solution was re-treated with charcoal, and concentrated to dryness in a water-bath at 60°, to give 1-methyl fructose as a sweet-tasting, honey-coloured, resinous syrup (270 g., 93%) (Found: OMe, 14·7. Calc. for $C_7H_{14}O_6$: OMe, 15·9%).

Crude " α "-*Diisopropylidene Fructose.*—(a) *From invert sugar.* Commercial invert sugar syrup (700 g.) was dried under reduced pressure on a steam-bath. To the viscous, almost solid resin so obtained (580 g.) acetone (4 l.) and anhydrous pulverized zinc chloride (700 g.) were added, together with coarse sand to facilitate disintegration of the resin. The mixture was stirred for 2 days at room temperature, by which time almost all the sugar had dissolved. Sodium hydroxide (450 g. in 450 ml. of water) was now added dropwise with cooling and the inorganic precipitate was collected and washed with acetone. The filtrate and washings were concentrated and the residue was diluted with water (500 ml.) and extracted with chloroform (4 × 200 ml.). The chloroform extracts were washed with water, dried (Na_2SO_4), and concentrated to give a residue of crude " α "-di*iso*propylidene fructose (250 g., 60% yield based on the fructose content of the invert sugar), m. p. 52—75°. This material was suitable for the preparation of 3-methyl di*iso*propylidene fructose as described below.

(b) *From sucrose.* A suspension of sucrose (250 g.) in acetone (1500 ml.) containing concentrated sulphuric acid (4·5 ml.) was stirred at room temperature for 2 days. The undissolved sugar (125 g.) was separated and the filtrate made alkaline with sodium hydroxide and concentrated. The residue was diluted with water and extracted with chloroform and the chloroform evaporated to give crude " α "-di*iso*propylidene fructose (137 g.) which probably contained considerable quantities of " β "-di*iso*propylidene fructose and di*iso*propylidene glucose but could be methylated as described below to give 3-methyl di*iso*propylidene fructose of good quality.

3-*Methyl Diisopropylidene Fructose.*—(a) *From pure* " α "-*diisopropylidene fructose.* A mixture of " α "-di*iso*propylidene fructose (52 g.; m. p. 115—117°), acetone (100 ml.), and pulverized sodium hydroxide (21·4 g.) was treated at 40—50°, with stirring, with methyl sulphate (28·4 ml., added dropwise during 75 minutes). Methylation was completed by warming at 50° for 90 minutes and finally at 55—60° for 3 hours. The sludge was diluted with water and extracted with chloroform, and the chloroform extracts were washed with water and concentrated to give 3-methyl di*iso*propylidene fructose (53 g.; m. p. 110—112°). One crystallization from hexane (200 ml.) gave 45 g. (82%), m. p. 113—117°.

(b) *From crude* " α "-*diisopropylidene fructose obtained from invert sugar.* The crude derivative (250 g.) was mixed with acetone (500 ml.) and sodium hydroxide (144 g.) and warmed with stirring to 45°. Methyl sulphate (183 ml.) was added at 40—50° during 75 minutes and methylation was completed by warming at 50° for 1 hour and finally at 55—60° for 3 hours. The crude product (272 g.), isolated as in (*a*), crystallized from hexane (300 ml.), to give 3-methyl di*iso*propylidene fructose (110 g., 42%; m. p. 115—117°).

(c) *From crude* " α "-*diisopropylidene fructose obtained from sucrose.* The crude material (137 g.) was methylated as in (*b*) with proportionate amounts of materials, and the crude product crystallized from hexane, to give 3-methyl di*iso*propylidene fructose (39·5 g.; m. p. 110—115°).

Hydrolysis of 3-*Methyl Diisopropylidene Fructose to* 3-*Methyl Fructose.*—(a) *By an acidic ion-exchange resin.* A mixture of 3-methyl di*iso*propylidene fructose (27·4 g.), ion-exchange resin (5 g.; Amberlite IR-120, acid form, Rohm and Haas Co., Philadelphia), and water (100 ml.) was stirred at 95—100° for 5—6 hours. The resin was then removed, and the solution decolorized with charcoal (4 g.) and

concentrated to a syrup which crystallized on being rubbed with acetone (35 ml.). This crystalline 3-methyl fructose (17·2 g., 89%; m. p. 119—121°) recrystallized from methanol and melted at 124—126°.

(b) *With water at* pH 2·6. 3-Methyl di*iso*propylidene fructose (27·4 g.) was digested for 5 hours on a steam-bath with 3 parts of water acidified to pH 2·6 with sulphuric acid. The hydrolysate was decolorized with charcoal and refined as in (*a*), to give 3-methyl fructose (18·2 g., 93%; m. p. 119—121°).

Mixtures of Approximately Equal Proportions of 1- *and* 3-*Alkyl Glucose from Sucrose.*—Mixtures of the alkyl hexoses (methyl, ethyl, and propyl) were prepared from sucrose by fission, treatment with acetone, alkylation, and hydrolysis by methods similar to those described above.

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573. *Hysteresis in Transitions in Solids.*

By D. G. THOMAS and L. A. K. STAVELEY.

It is pointed out that in transitions in solids hysteresis seems to be confined to those cases in which part, at least, of the change occurs almost isothermally, *i.e.*, to those in which there is a stage in the transition when a new phase has to develop in one physically distinct from it. The theory of nucleation proposed by Turnbull has been applied to such transitions. The essential idea is that the initial development of the new phase is hindered both by the interphase-surface free energy and by the strain to which the growing nucleus is subjected, so that the temperature at which the two phases have the same molar free energies in bulk must be passed before the difference in bulk free energy outweighs the surface and strain effects and makes possible the appearance, at an observable rate, of self-propagating nuclei.

The difficulties in the quantitative application of the theory are considered, but estimates are made of the range in which surface free-energy values would have to fall to account for observed hysteresis effects.

The theory has been qualitatively used in a consideration of the factors which affect the width of hysteresis loops and the sharpness with which transitions set in, and also of observed phenomena within the loops.

A CONSIDERABLE number of transitions in solids exhibit hysteresis in the sense that part or all of the change sets in on warming at a temperature T_w, which is higher than that, T_c, at which this change begins on cooling. A schematic plot of volume against temperature for such a transition is shown in Fig. 1. For some transitions the difference $T_w - T_c$ may be as little as $\sim$0·05°, but for others it may be a hundred or even a thousand times greater. The most detailed studies of this hysteresis have been carried out with molecular and ionic solids, in which equilibrium in the transition region is much more rapidly established than in alloy systems.

We shall classify transitions in solids into three types. Type I are those which occur continuously throughout. Type II are those in which part of the transition is gradual and part isothermal. (Transitions of types I and II are what have been loosely termed second-order or "lambda-point" transitions.) Type III are those normally regarded as first-order phase changes which apparently occur completely isothermally. We must emphasise that we have introduced this classification primarily for convenience; experimentally it may be very difficult to classify a particular transition on this basis, and moreover it is possible that distinction between types II and III is artificial, in that very careful studies of apparently first-order transitions may reveal phenomena analogous to premelting, in which event type III merges into type II (Mayer and Streeter, *J. Chem. Physics*, 1939, **7**, 1019). (It may be mentioned that fusion is normally regarded as a type III phase change, although there is now a considerable amount of experimental evidence that it is preceded by genuine monophase premelting.) Previous studies of hysteresis have been largely confined to transitions of types I and II, so that the impression has been gained that hysteresis is associated only with transitions which are at least partly gradual. We shall endeavour to show, however, that for hysteresis to appear

at all it is essential that part at least of the transition should be isothermal, and that the hysteresis is confined to this isothermal part of the change. In contrast, the completely gradual transitions of type I are hysteresis-free.

We must briefly consider whether or not the curves of Fig. 1 can be regarded as equilibrium curves. In the systems which we shall treat, all attempts to eliminate the hysteresis have failed; these include waiting for long periods, inoculation, agitation with supersonic waves, and carrying out the transition in presence of a solvent (Staveley, *Quart. Reviews*, 1949, **3**, 65). Nevertheless we must accept that, if a transition involves a change from one distinct phase into another, then these two phases can only be *in equilibrium when present in bulk in a normal unstrained state* at one temperature at a given pressure: we shall call this temperature T_e. We must therefore conclude that one or both of the temperatures T_w and T_c do not coincide with T_e, and the reason for this constitutes the problem discussed below.

So far as we are aware, two theories have been proposed dealing explicitly with hysteresis in transitions in molecular and ionic solids, one by Schäfer (*Z. physikal. Chem.*, 1939, **44**, *B*, 127) and the other independently by Dinichert (*Helv. Physica Acta*, 1944, **17**, 389), and by Frank and Wirtz (*Naturwiss.*, 1938, **42**, 687).

The essential idea of the first is that the unit in terms of which the transition must be considered is not the whole crystal, but a domain ("Bezirk") consisting of relatively very few molecules; the properties of the system as a whole then depend on the characteristics of the average domain, which in turn depend on domain size. When the system is cooled, the transition occurs in a small temperature range, producing initially very small domains of the low-temperature form which are assumed to amalgamate below the transition to larger domains, which, in consequence of the dependence of energy parameters on domain size, undergo the reverse change on warming at a higher temperature.

Dinichert, and Frank and Wirtz, suggested that, as a consequence of the different densities of the two phases, regions of one phase growing within the other are subject to strain, and that this strain changes the transition temperature in accordance with the Clapeyron–Clausius equation.

While we do not consider either of these theories to be wholly satisfactory, we think it true that, on the one hand, in phase transitions the change developing from any one nucleus may well be limited to a very small region, and on the other, strains arising from density differences contribute to the free-energy relations in the transition region.

In their treatment of order–disorder in alloys, Bragg and Williams (*Proc. Roy. Soc.*, 1934, *A*, **145**, 699) pointed out that it appeared to follow that, if the change was partly isothermal, the temperature of this abrupt part would be different on heating and cooling. [Later, Frank (*ibid.*, 1939, *A*, **170**, 182) attempted to explain the supercooling of liquids on this basis.] Bragg and Williams, however, themselves doubted whether their conclusion was physically significant.

It seems to us that hysteresis arises from the well-known difficulty attendant upon the initial appearance of one phase within another. Recently this process of nucleation in solids has been quantitatively treated by Fisher, Holloman, and Turnbull (*J. Appl. Physics*, 1948, **19**, 775), and while it seems they had in mind primarily metallic systems, and although they did not explicitly consider hysteresis, we think that their treatment may be applied to hysteresis phenomena in solids. Ideas similar to those inherent in their treatment have been put forward, but not developed, by Baker and Smyth (*J. Amer. Chem. Soc.*, 1939, **61**, 2798) (see also Ubbelohde, *Trans. Faraday Soc.*, 1937, **33**, 1203).

We regard the gradual part of a transition as representing a growth of disorder throughout the crystal as a whole, which in a type I transition proceeds continuously to completion. In a type II transition the isothermal part must be considered on a different basis, namely, as involving the formation and development of nuclei of one phase within another physically distinct from it.

Following Fisher, Holloman, and Turnbull (*loc. cit.*) we may write the free-energy increase, consequent on the formation of a nucleus of i particles of one phase within another, as:

$$\Delta F_i = Ai^{2/3} + Bi + Ci \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The term $Ai^{2/3}$ represents the contribution of the interfacial free energy of the two phases, on the assumption that the nucleus has such a shape that its surface is proportional to $i^{2/3}$. (In general we suppose A to be positive; we briefly consider below the possible consequences of this not being so.) In Bi, B is the free-energy difference of one mole of the two phases at a particular temperature, divided by the Avogadro number; in future we shall refer to this as the bulk free-energy term. The term Ci represents the increase of free energy consequent on

the fact that the two phases have different densities and are to some extent rigid, so that the nuclei will be in a state of strain. The free-energy term due to strain will depend in addition on the shape of the nucleus, and its dependence on the size will be more complicated than simple proportionality, especially when i becomes large.

Below T_e, the true equilibrium temperature at which B is zero, all terms in (1) are positive; when $T = T_e$ the formation of nuclei will still be associated with an increase of free energy due to the A and the C term. When T is greater than T_e, B is negative and increases numerically with rising temperature. If equation (1) is taken literally, at first, just above T_e, $B + C$ will be positive, so that at a particular temperature ΔF_i increases indefinitely with i; however, C probably declines when i becomes large, and, as assumed by Fisher *et al.*, ΔF_i will pass through a maximum as i increases. The value of i, which corresponds to a nucleus of critical size which can grow with a decrease of free energy, will occur at smaller i values as T increases and B becomes greater.

Not until a nucleus of such critical size has appeared within a crystal unit does the bulk transformation of that unit become possible. Similar considerations will apply when the high-temperature form is cooled below T_e. We consider that herein lies the origin of hysteresis; it arises because, for a range of temperature near T_e, the chance of formation of such a nucleus is negligible.

FIG. 1.

Schematic representation of the change in volume for ascending and descending temperature in a type II transition.

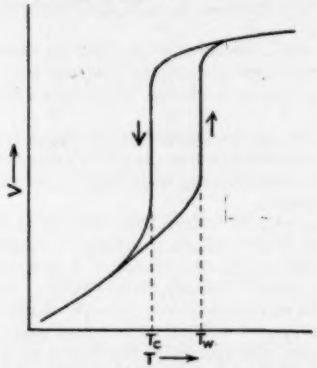
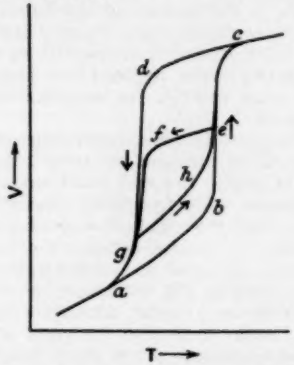


FIG. 2.

The change in volume with temperature starting from points lying on the boundaries of a hysteresis loop.



By applying the theory of absolute reaction rates, Turnbull and Fisher (*J. Chem. Physics*, 1949, **17**, 71) have derived the following approximate expression for the rate of nucleation in supercooled liquid metals:

$$r^* \approx \frac{NkT}{h} \cdot \exp\left(-\frac{\Delta F_A}{kT}\right) \cdot \exp\left(-\frac{\Delta F_i^*}{kT}\right) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where r^* is the number of nuclei capable of self-propagation formed per mole per sec., ΔF_A is the free energy of activation for the transport of one atom across the interface of the two phases, and ΔF_i^* is the free energy of formation of a nucleus of critical size. For nucleation in liquid metals they have assumed that ΔF_A is about the same as the free energy of activation for viscous flow. The value of ΔF_A is such that the rate of change of the first exponential term with temperature could not possibly account for the extraordinarily large temperature dependence of r^* which is actually observed. (Thus, for mercury, no detectable nucleation occurs for about 60° below the melting point, but when the rate eventually becomes measurable it alters by a factor of about ten for a change of temperature of 1·5°.) As Turnbull has pointed out, this extreme sensitivity to changes of temperature arises essentially from the variation of ΔF_i^* with temperature. We consider that the same is true for our systems also; ΔF_i^*, and *not* an activation energy ΔF_A controlling nuclear growth, is responsible for hysteresis.

By differentiating (1) with respect to i and equating $d\Delta F_i/di$ to zero, we find that the maximum value of ΔF_i is:

$$\Delta F_i^* = 4A^3/[27(B + C)^2] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Turnbull and Fisher, considering nucleation in liquids, for which the C term vanishes, assumed the nuclei to be spherical and the entropy of fusion to be independent of temperature. ΔF_i^* at $\Delta T°$ below T_0, the melting point, then becomes :

$$\Delta F_i^* = 16\pi\sigma^3 T_0^2/3\lambda^2(\Delta T)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where σ is the interfacial-surface free energy per unit area, and λ is the latent heat of fusion per unit volume. Turnbull and Fisher used the value of ΔF_i^* given by (2) in equation (4); $\frac{NkT}{h} \cdot \exp\left(\frac{-\Delta F_A}{kT}\right)$ was estimated to be about 10^{35}. The observed rate of nucleation in small liquid drops was such that $\exp(-\Delta F_i^*/kT)$ was then required to have a value of about 10^{-37}.

In attempts to apply these calculations to our systems a number of difficulties arise; we cannot be sure of the applicability of the theory of absolute reaction rates to such systems; even if its application is valid, we are ignorant of ΔF_A. Moreover we do not know the average size of the crystal unit in which we have to consider the formation of a single nucleus. Furthermore, the strain term does not vanish and is difficult to estimate. In view of these uncertainties, we will provisionally neglect the strain term and estimate the values of σ for a range of values of $\exp(-\Delta F_i^*/kT)$, choosing values of ΔT representative of hysteresis loops in transitions in molecular and ionic solids, and then we will form an estimate of the sensitivity of rate of nucleation to temperature variation.

We may consider, as roughly typical of average behaviour, an imaginary transition for which T_0 is about 300° K., at which temperature the heat absorbed is 300 cals./mole, and we will suppose the molar volume, V, to be 30 c.c., so that λ is 10 cals./c.c.

In Table I are recorded the values of σ which satisfy equation (4), for three arbitrary values of ΔT and for the three values of ΔF_i^* corresponding to $\exp(-\Delta F_i^*/kT) = 10^{-10}$, 10^{-20}, and 10^{-50}.

TABLE I.

Values of σ *in ergs/cm.*^{2} *calculated from equation* (4) *with* $T_0 = 300°$ K., $\lambda = 10$ *cals./c.c., for* $\Delta T = 0{\cdot}1°$, $1{\cdot}0°$, $10°$, *and for the values of* ΔF_i^* *corresponding to* $\exp(-\Delta F_i^*/kT) = 10^{-10}$, 10^{-20}, *and* 10^{-50}.

$\exp(-F_i^*/kT)$.	$\Delta T = 0{\cdot}1°$.	$\Delta T = 1{\cdot}0°$.	$\Delta T = 10°$.
10^{-10}	0·10	0·48	2·2
10^{-20}	0·15	0·69	3·2
10^{-50}	0·18	0·82	3·8

In order to compare directly the magnitudes of the surface and bulk-energy terms, following Turnbull we may approximately transform the σ values into cals./mole by multiplying by $N^{\frac{1}{3}}V^{\frac{2}{3}}/4{\cdot}2 \times 10^7 \simeq 19{\cdot}5$. The extreme values of σ recorded in Table I then correspond to ~2 and 74 cals./mole, or ~0·7 and 13% of the heat of transition. So far as we know, there are no independent estimates of σ; the range of percentages quoted is well below the values calculated by Turnbull and his co-workers for nucleation in liquid metals, which are mostly between 30% and 50% of the molar heat of fusion. There is no reason to suppose, however, that interface relations in wholly solid systems must closely parallel those in solid–liquid systems; for example, there is the possibility with the former that the boundary between the two phases is not sharp but takes the form of a gradual change over a number of molecular diameters, in order to make the interfacial free energy as small as possible (cf. Bloch walls in ferromagnetics).

Table II shows how, for the σ values of Table I which correspond to $\Delta T = 1°$, the quantity $\exp(-\Delta F_i^*/kT)$, *i.e.*, the rate of nucleation, alters with slight temperature changes.

TABLE II.

Values of $-\log[\exp(-\Delta F_i^*/kT)]$ *calculated for values of* σ *corresponding to* $\Delta T = 1°$, *for values of* ΔT *between* 0·9° *and* 1·1°.

σ.	$\Delta T = 0{\cdot}90°$.	$\Delta T = 0{\cdot}99°$.	$\Delta T = 1{\cdot}00°$.	$\Delta T = 1{\cdot}01°$.	$\Delta T = 1{\cdot}10°$.
0·48	12·3	10·2	10	9·8	8·25
0·69	37	30·6	30	29·4	24·8
0·82	61·6	50·8	50	49·1	41·2

It is clear from Table II that the theory can account for extremely rapid changes in the rate of nucleation with temperature. Thus if we take $\exp(-\Delta F_i^*/kT)$ to be 10^{-30} when $\Delta T = 1°$, a change of only 0·02° (from $\Delta T = 0{\cdot}99°$ to $\Delta T = 1{\cdot}01°$) changes the rate of nucleation by a factor of 10^{14}, *i.e.*, about 16, and a change of 0·2° by ~10^{12}. Thus, though the new phase

cannot literally appear suddenly at a particular temperature, this clearly is very much the impression one would get in an experimental investigation.

If in the above example ΔT had been taken to be 0·1° instead of 1·0°, the change of rate of nucleation by a factor of 16 (in the first case produced by a change in ΔT of 0·02°) would now be produced by an alteration in ΔT of only 0·002°, and similarly for $\Delta T = 10°$ the corresponding figure is 0·2°.

We may conclude therefore that, if we disregard any other factors (*e.g.*, impurities, particle size, etc.) which may influence the sharpness of a transition, then, for a group of transitions in different solids for which $\exp(-\Delta F_i^*/kT)$ has about the same value, T_w and T_c would be more precisely defined the narrower the hysteresis loop. There are not sufficient data on rates of attainment of equilibrium to enable this conclusion to be tested. But it may be worth noting that a consideration of transitions in similar substances does give the impression that the maximum rate of volume change (relative to the total volume change) with temperature is greater the narrower the hysteresis loop. [In particular, it is rather striking that for tetradeuterammonium bromide this rate for the upper of the two transitions, which has a very narrow hysteresis loop, is some 10—20 times greater than that for the lower one where the loop is unusually wide (Smits, Tollenaar, and Kröger, *Z. physikal. Chem.*, 1938, **41**, *B*, 215).]

Hitherto we have neglected the strain term; an upper limit of the magnitude of this may be very roughly estimated by assuming that a nucleus of one phase in another is either compressed or extended, so that it occupies the same volume as the same mass of the second phase. On this basis

$$\Delta F_i^* = \frac{16\pi\sigma^3}{3\left\{-\frac{\lambda\Delta T}{T_0} + \frac{1}{2\beta}(\delta V)^2\right\}^2} \qquad \ldots\ldots\ldots (5)$$

If we take β, the isothermal compressibility, to be 5×10^{-6} atm. and δV, the volume change per unit volume at the transition, to be 0·003 (these figures are roughly those for the transition in ammonium chloride), $\frac{1}{2\beta}(\delta V)^2$ equals 0·02, while $\lambda\Delta T/T_0 = 0{\cdot}03\ \Delta T$. Although this is probably an overestimate of the effect of strain, it is clear that this effect could be important. It will operate to reduce the calculated values of σ, and it will also enhance the sensitivity of the dependence of nucleation rate on temperature.

Since strain effects broaden the hysteresis loop, one might enquire whether there is any correlation between ΔV, the value of the comparatively abrupt part of the volume change, and $T_w - T_c$ for transitions in a series of solids which have roughly the same values of β and of λ. The available data for ammonium salts are summarised in Table III. The values of ΔV can only be assessed very roughly. It will be seen that it is broadly true that the greater ΔV the greater $T_w - T_c$.

TABLE III.

ΔV *Values in c.c./mole for various transitions in ammonium salts occurring at* T_w, °K., *compared with the width of the hysteresis loop,* $T_w - T_c$.

Salt.	ΔV.	$T_w - T_c$.	T_w, °K.	Ref.
NH_4Br	0·03	0·06°	234·4	*A*
NHD_3Cl	0·07	0·07	247·95	*B*
ND_4Br	0·08	0·11	214·89	*C*
NH_3DCl	0·11	0·12	244·61	*B*
NH_4Cl	0·15	0·35	242·61	*B*
$(NH_4)_2SO_4$	0·35	1·2	223·40	*D*
ND_4Br	0·6	9·0	168·1	*C*
8·5% NH_4Br + 91·5% NH_4Cl	0·65	14·6	232·5	*E*
11·6% NH_4Br + 88·4% NH_4Cl	1·09	20·0	212·2	*E*

References: *A*, Smits, Ketelaar, and Müller, *Z. physikal. Chem.*, 1936, **175**, *A*, 359. *B*, Thomas and Staveley, *loc. cit.* *C*, Smits, Tollenaar, and Kröger, *Z. physikal. Chem.*, 1938, **41**, *B*, 215. *D*, Hogg and Staveley (unpublished). *E*, Mandelberg and Staveley, *J.*, 1950, 2736.

We shall now examine in greater detail the available experimental data, beginning with those which bear on the correlation of the sharpness of transition with the presence of hysteresis. Strictly speaking, no part of a transition is observed to occur completely isothermally, just as the melting point of a substance always shows some drift as melting proceeds. No doubt, just as in melting, impurities will tend to make a transition less abrupt, and in addition for solid–solid transitions other factors will produce the same result. Thus T_w and T_c can vary

with particle size (Thomas and Staveley, *J.*, 1951, 1420), so that non-uniformity of crystal size will be such a factor; different crystals being in different states of strain may lead to transformation at different temperatures. In calorimetric work, electrical heating can result in local overheating and cause a part of a sample to undergo a transition before the main body, and in the region of a hysteresis loop this is an irreversible process. Nevertheless it is difficult to resist the impression given by careful studies of transitions showing hysteresis (Staveley, *loc. cit.*) that part at least of these would occur isothermally in ideal circumstances, and moreover that hysteresis is associated primarily with the almost sharp, and not with the gradual, part of the transitions. Examples of transitions to which this statement applies occur in ammonium chloride, monodeuterammonium chloride, trideuterammonium chloride, ammonium sulphate, tetradeuterammonium sulphate, hydrogen sulphide, deuterium sulphide, ammonium bromide, and tetradeuterammonium bromide; further examples can be found in organic solids where the transitions have been studied by dielectric-constant measurements (see, *e.g.*, Crowe and Smyth, *J. Amer. Chem. Soc.*, 1950, **72**, 4009).

By contrast those transitions which are continuous throughout are quite free from hysteresis. Examples are not numerous but the transitions in sodium nitrate (Kracek, *J. Amer. Chem. Soc.*, 1931, **53**, 2609), ammonium iodide, and tetradeuterammonium chloride are certainly of this type; and the same is probably true of those in basic beryllium acetate between 30° and 40° (Jaffray, *Ann. Physique*, 1948, **3**, 5) and in copper sulphate pentahydrate (Brun and Jaffray, *Cah. Phys.*, 1944, **21**, 25).

An apparent exception to our generalisation that sharpness and hysteresis go together is provided by the transition in hydrogen bromide at about 90° K. Hysteresis is present here and is certainly associated with that part of the transition where the physical properties are changing most rapidly, but at no temperature does the heat content or dielectric constant change abruptly (Damkohler, *Ann. Physik*, 1938, **31**, 76; Eucken and Güttner, *Gottingen Nachr., Math.-Phys. Kl.* II, 1936, **2**, 167). Perhaps the same is true of the transition in methane where only heat capacity has been measured (Eucken and Bartholomé, *ibid.*, 1936, **2**, 51).

As we shall discuss below, there is evidence that the hysteresis characteristics in certain systems do not become reproducible until they have been subjected to the transition many times. In the light of this and of what has already been said about the factors that tend to make a sharp transition apparently diffuse, we consider that in spite of these apparently anomalous phenomena the generalisation is still of value.

The transitions exhibiting hysteresis which have been most carefully studied are of type II. With regard to type III (first-order) transitions, it is usually supposed that the steady temperature attained when one form is produced from the other, either in heating or in cooling, is the true equilibrium temperature; the supercooling of the high-temperature form below this temperature is a common phenomenon. Superheating of the low-temperature form above T_e has been more rarely observed, *e.g.*, with α–β-sulphur. Perhaps the most complete investigation of these effects is that carried out by Wiebenga (*Z. anorg. Chem.*, 1935, **225**, 38) on hexachloroethane which has two type III transitions. For each of these he established T_e by finding the temperature at which, with two phases present, the interconversion rate was zero. For each transition, T_e is certainly above the temperature at which the change sets in on cooling and, for the lower transition at least, T_e may be lower than the temperature at which the change takes place on warming. Although more experimental evidence is needed it seems clear that many type III transitions display hysteresis, at least in one direction (*i.e.*, either $T_w > T_e = T_e$ or $T_e < T_w = T_e$), if not in both (*i.e.*, $T_e > T_e > T_w$) (see, for instance, Smyth, *loc. cit.*, and Connell and Gammel, *Acta Cryst.*, 1950, **3**, 75).

It is possible that in some systems factors which we have not yet considered come into play and modify the conclusion reached from the theory outlined above, namely, that all type III and type II transitions should show hysteresis in both directions. It may be possible for nuclei of the high-temperature modification, at least, to form most easily on the crystal surface (cf. fusion); this could prevent T_w from rising above T_e, but, on cooling, nucleation would then presumably have to start within the crystals leading to hysteresis on cooling (cf. the solidification of liquids).

Another factor is that, whereas we have supposed hitherto that the formation of an interface between two phases is accompanied by a free-energy increase, it is possible that the reverse may sometimes be true and so hysteresis could vanish on the basis of the theory given above. (The mathematical formulation would now be different since the nuclei would no longer be spherical.) Further, a negative surface free energy will tend to make the interfacial surface area as large as possible; this will lead in the limit to the growth of order or disorder homo-

geneously throughout the crystal. The transition could then be completely gradual (type I) (cf. Mayer and Streeter, *loc. cit.*) and, as we have seen, such transitions appear to be hysteresis-free.

We shall now consider the relation between the two phases at temperatures between T_v and T_e. From experiments, particularly by Smits and his co-workers, it appears that the curve obtained on warming to some point *b* (Fig. 2), before the really rapid volume alteration sets in, is completely reversible on cooling from *b*; the same applies on cooling to *d* and then warming. On warming to *e* and then cooling, however, a path such as *efga* is followed, and on warming from *g* a path such as *ghc*. Furthermore, it is possible to stop on such curves as *efg* or *ghc*. Moreover, although equilibrium is usually quickly attained along curves *ab* and *cd*, along *bc* and *da* it may be only very slowly reached. One must assume that points on *bc* and *ad* and within the loop represent a mixture of the two forms. If there is some mechanism of transference between the two phases they can co-exist in equilibrium only at one temperature T_e. For systems which give curves as in Fig. 2 we must conclude that such a mechanism is absent. This is comprehensible if a whole crystal can change without influencing its neighbours, and if, after a self-propagating nucleus has appeared in a single crystal unit, the whole unit changes almost at once (it may be that the crystal unit in this sense is very small). Thus at the point midway between *b* and *c* half the crystal units are at *c* and half at *b*; on cooling, those at *c* follow the path *cdga*, the others the curve *ba*, so that the observed curve *efg* is a weighted mean of these two limiting curves. Observations of V–T relationships within hysteresis loops are essentially consistent with this picture, but we cannot rule out the possibility that circumstances may arise in which transference is possible between the two forms and in which the change spreads only slowly from a nucleus, so that the two forms co-exist within the same crystal unit over an appreciable time. Thus, if for such a system in which equilibrium between the two modifications can be easily attained, T_e is very near T_v, then on cooling from *e* the path followed will be near the curve *eba*, and the hysteresis on cooling will only be apparent if the system is first heated so that the transformation to the high-temperature form is complete.

The transition in ammonium chloride must presumably be one in which the transformation takes place in small crystal units between which there is no interaction, for, with both forms present, the transformation velocity is immeasurably small inside the loop. With ammonium chloride it is not hard to understand why the phase change, once initiated, should be very rapid, for over the whole transition the ammonium ions can execute to some extent the motion required to bring about the final sudden change.

Rather similar observations have been made by Bridgman in his studies of transitions under high pressures. (Just as thermal hysteresis occurs at constant pressure, so also hysteresis is possible when the pressure is varied at constant temperature.) For some transitions at constant temperature he found a " region of indifference "—that is, a region of pressure in which the interconversion velocity was apparently zero even though both forms were present (Bridgman, " The Physics of High Pressures," G. Bell and Sons, 1931).

We have already mentioned the possibility that nucleation may commence on the crystal surface; in this event one must expect that, in principle, particle size would influence the hysteresis characteristics. In fact, for extremely small crystals of ammonium chloride the loop is slightly narrower than for larger crystals (Thomas and Staveley, *loc. cit.*). One could also imagine that the nature of the medium in contact with the crystal surface might influence the hysteresis loop; experiments in this laboratory (to be more fully reported later), in which the transition in ammonium chloride has been studied dilatometrically in a variety of fluids, showed that with the most polar liquids used (mixtures of methyl alcohol and water) the loop is appreciably wider: it is interesting that the hysteresis persists in methyl alcohol–water mixtures in which ammonium chloride is appreciably soluble. One must therefore suppose that even under these conditions transference between the two forms is very slow.

It has been observed that as a substance is repeatedly subjected to a transition the hysteresis loop sometimes becomes narrower, until a limiting condition is reached. This may be due to a progressive break-up of the crystals, and in this connection the following point may be noted. If, on the first occasion on which the substance is subjected to the transition, the crystal units are relatively large, it is then possible that in some of these more than one self-propagating nucleus could develop. Wherever this produces a form with some particular orientation between molecules and ions, the ordered regions arising from these nuclei will eventually meet and form interfaces at which the orientation of the particles concerned may change, so that the particles break up. In a repetition of the experiment, the transition is then being studied with smaller crystal units, so that the width of the loop is slightly changed.

Clusius and Weigand (*Z. Elektrochem.*, 1938, **44**, 674) found that increase of pressure broadens the hysteresis loop in the III ⇌ II transitions in hydrogen and deuterium sulphides; in view of the very sensitive dependence of the intermolecular forces on distance, this may be caused by an increase in the interfacial free energy as the molecules are brought together.

Finally, we may observe that small quantities of impurities have relatively little effect on hysteresis phenomena in solid–solid transitions. This is in contrast to the solidification of supercooled liquids where a nucleus, the formation of which has arisen from some impurity, can result in the crystallisation of the whole mass (cf. Turnbull and Cech, *J. Appl. Physics*, 1950, **21**, 804). If in solid–solid transitions, as we believe, the change takes place in comparatively small unconnected crystal units, then the induction of nucleation in a few of these by chance impurities will not affect the behaviour of the majority.

We thank Mr. R. P. Bell for reading and commenting on the manuscript.

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574. *The Seed Fat of* Parinarium laurinum. *Part III.** *Catalytic Hydrogenation of Methyl Parinarate.*

By J. P. RILEY.

The hydrogenation of methyl parinarate at 100° in the presence of Raney nickel catalyst has been followed spectrophotometrically. It has been found that the primary reaction consists of the simultaneous addition of either two or three molecules of hydrogen, yielding non-conjugated methyl octadienoates (containing the unsaturated system $-CH{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH-$) and methyl octadecenoates respectively. Only comparatively small amounts of conjugated methyl octadeca-dienoates and -trienoates are formed. The hydrogenation is extremely selective; very little methyl stearate is formed until all the parinarate, conjugated esters, and non-conjugated methyl octadienoates have been converted into methyl octadecenoates.

IN the earlier papers of this series (*J.*, 1950, 12; 1951, 291) the constitution of the acids and glycerides of the seed fat of *Parinarium laurinum* has been described. It was shown that the mixed acids from the fat contained *ca.* 55% of parinaric acid (octadeca-9 : 11 : 13 : 15-tetraenoic acid †). Since the mechanism of hydrogenation of a conjugated tetraene does not yet appear to have been studied it was thought be of interest to prepare pure methyl parinarate and submit it to catalytic hydrogenation.

Methyl parinarate was hydrogenated at 100° in presence of Raney nickel as catalyst, fractions being removed at 20, 35, 50, 65, and 80% saturation. These fractions were analysed spectrophotometrically for methyl parinarate and conjugated methyl octadeca-dienoate and -trienoate as described in Part I. In Table I are recorded the extinction coefficients used in the calculations.

TABLE I.

Extinction coefficients used in calculations.

	$E^{1\%}_{1\,cm.}$* at		
	234 mμ	270·5 mμ	305 mμ
Methyl parinarate	74·3	408	2630
Conjugated methyl octadecatrienoate	208	1780	—
Conjugated methyl octadienoate	1200	—	—

(* Expressed as acids.)

In Fig. 1 is shown the general effect of hydrogenation on the absorption spectrum of methyl parinarate. Clearly this indicates progressive removal of conjugated tetraenes with insignificant production of conjugated triene or conjugated diene esters.

* Part II, *J.*, 1951, 291. † Geneva system, CO_2H = 1.

Methyl stearate was determined in the later fractions by acetone–permanganate oxidation, and non-conjugated octadecadienoates and octadecenoates were determined from the amount of hydrogen which had been absorbed, allowance having been made for the other unsaturated esters present. It is not claimed that these results are of a high degree of accuracy, but it is impossible to use normal iodine-value methods for the measurements of the unsaturation of conjugated unsaturated systems, and even Toms's bromine absorption method (*Analyst*, 1928, **53**, 69) which gives theoretical values with methyl elæostearate yields results with methyl parinarate which are rather variable and low by about 25%. Fraction 5 in which the proportion of conjugated esters was negligible was calculated from the Wijs iodine value.

The results of these determinations are shown diagrammatically in Fig. 2 (cf. Table III). They indicate that the principal products of the hydrogenation in the initial stages are non-

FIG. 1.

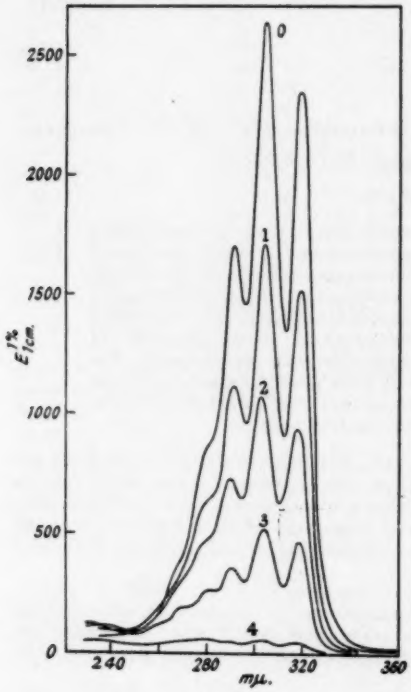
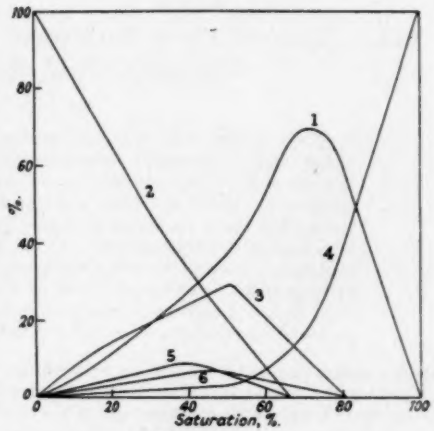


FIG. 2.



1 = *Monoene.*
2 = *Parinaric acid.*
3 = *Non-conjugated diene.*
4 = *Saturated.*
5 = *Conjugated triene.*
6 = *Conjugated diene.*

conjugated methyl octadecadienoates and octadecenoates formed by the simultaneous addition of either two or three molecules of hydrogen respectively. Only small amounts of conjugated dienoates and trienoates are formed. Comparatively little methyl stearate is formed until all the esters with two or more double bonds have been converted into methyl octadecenoates.

Three non-conjugated methyl octadecadienoates are theoretically obtainable by the hydrogenation of methyl parinarate (assuming, as is probable, that no double bond shift takes place on hydrogenation at 100° with Raney nickel) :

$CH_3 \cdot [CH_2]_3 \cdot CH{=}CH \cdot [CH_2]_3 \cdot CH{=}CH \cdot [CH_2]_7 \cdot CO_2Me$ (I.)
$CH_3 \cdot CH_2 \cdot CH{=}CH \cdot [CH_2]_3 \cdot CH{=}CH \cdot [CH_2]_6 \cdot CO_2Me$ (II.)
$CH_3 \cdot CH_2 \cdot CH{=}CH \cdot [CH_2]_4 \cdot CH{=}CH \cdot [CH_2]_7 \cdot CO_2Me$ (III.)

Ozonolysis of the hydrogenation fraction 2, which contained 20·6% of non-conjugated dienoates, yielded succinic acid, but no adipic acid, indicating that esters of the structures (I) and (II) were present.

Fractions 3 and 5 (50% and 80% saturation respectively) were submitted to acetone–permanganate oxidation and the recovered dibasic acids were separated by fractionation of their dimethyl esters with the results summarised below.

	Dibasic acids, % (mol.)			
Fraction	C_9	C_{11}	C_{13}	C_{15}
3	37	21	21	21
5	12	54	25	9

The high proportion of azelaic acid (C_9) formed from fraction 3 is due to the 20% of unchanged unhydrogenated methyl parinarate which it contains. These data enable the approximate proportion of hydrogen addition at the various double bonds to be estimated. If the small amounts of conjugated diene and triene esters present are ignored, it may be seen that undecane-dicarboxylic acid must be formed either from the diene (II), or from the octadec-11-enoate formed either from (II), or directly from methyl parinarate by addition of 3 molecules of hydrogen. Similarly tridecanedicarboxylic acid is formed from methyl octadec-13-enoate, which may result either by simultaneous addition of 3 molecules of hydrogen to methyl parinarate or by partial hydrogenation of the diene (I). Pentadecanedicarboxylic acid can only be formed from octadec-15-enoic acid which must have been produced by the addition of 3 molecules of hydrogen to the 9, 11, and 13 double bonds. In the case of fraction 5, it is not possible to determine whether the high proportion of undecanedicarboxylic acid found is not in error owing to the difficulty of separating dibasic acids by fractional distillation.

It is interesting to compare the hydrogenation of methyl parinarate with that of methyl elæostearate (methyl octadeca-9 : 11 : 13-trienoate) which has been investigated by a number of workers, the most recent being Hilditch and Pathak (*Proc. Roy. Soc.*, 1949, *A*, **198**, 323), who confirmed the findings by Groot, Kentre, and Knol (*Rec. Trav. chim.*, 1947, **66**, 633) that the primary reaction is the simultaneous addition of two molecules of hydrogen to one molecule of elæostearate with the formation of considerable quantities of methyl octadeca-11-enoate. This reaction is quite analogous to the addition of two molecules of hydrogen to one molecule of methyl parinarate with the formation of the non-conjugated octadecadienoates (I) and (II).

The hydrogenation of methyl parinarate is even more selective than that of methyl elæostearate, since for example at *ca.* 50% saturation only 3·5% of methyl stearate was formed from the former compared with 13·5% from methyl elæostearate.

Experimental.

Preparation of Methyl Parinarate.—The seed fat of *P. laurinum* (230 g.) was hydrolysed by boiling it for 30 minutes with 10% alcoholic potassium hydroxide (1 l.), and the product poured into a large amount of water. The acids were liberated from the soaps with sulphuric acid and extracted with ether as rapidly as possible to prevent oxidation. After removal of the ether, the mixed fatty acids (210 g.) were crystallised twice from light petroleum (b. p. 40—60°) (2·5 l.) first at −20° and then at 0°. The resultant crystals were recrystallised from ether at −20° and then at −15° and yielded parinaric acid (67·6 g.), m. p. 86°, sap. equiv. 274·8 (Calc. for $C_{18}H_{28}O_2$: 276).

The purified parinaric acid (48·0 g.) was esterified at room temperature with 500 ml. of methyl alcohol containing 0·5% of hydrogen chloride and yielded, after removal of free acid, white crystals of methyl parinarate (47·5 g.), m. p. 34—35°, n_D^{40} 1·5567, I.V. (Wijs on 0·1 g. for 30 minutes) 194·3; I.V. (Toms) 272·0, $E_{1\,cm.}^{1\%}$ at 305 mμ. 2630, at 270·5 mμ. 408, and at 234 mμ. 74·3.

Table II.

Fractions of hydrogenated esters.

		Hydrogenated,*	I.V.	I.V.		$E_{1\,cm.}^{1\%}$ at (mμ.)†		
No.	G.	%	(Wijs)	(Toms)	n_D^{40}	234	270·5	305 ‡
0	44·3	0	194·3	272·0	1·5567	74·3	408	2630
1	4·84	20	176·2	259·9	1·5180	99·4	355	1711
2	4·73	35	156·3	198·5	1·4949	107·0	317	1048
3	14·76	50	128·5	166·4	1·4720	106·6	192	509
4	5·03	65	95·0	100·1	1·4510	50·8	53·7	47·1
5	15·07	80	50·4	47·5	1·4438	6·2	5·4	1·5
Total	44·43							

* Expressed as percentage of the volume of hydrogen required for complete saturation (14·02 l. at 19°/790 mm.). † Expressed as acids.

‡ Value at band head; actual positions of bands vary slightly.

TABLE III.

Composition of fractions.

No.	Hydrogenated, %	Parinaric acid	Conj. triene	Conj. diene	Non-conj. diene	Monoene	Satd.
0	0	100	—	—	—	—	—
1	20	65·0	4·7	3·7	14·7	11·9	—
2	35	39·0	8·5	5·1	20·6	26·0	—
3	50	19·3	6·3	6·7	29·0	35·3	3·4
4	65	1·8	2·6	3·7	15·4	64·5	12·0
5	80	0·1	0·3	0·5	—	59·3	39·8

TABLE IV.

(a) *Fractionation of methyl esters of water-soluble dibasic acids* L_1.

No.	G.	B. p./*ca.* 1 mm.	Sap. equiv.		Dibasic esters: C_9	C_{11}	C_{13}
1	0·119	<104°	104·6		0·119	—	—
2	0·265	104	104·9		0·265	—	—
3	0·278	104	104·3		0·278	—	—
4	0·258	104	104·9		0·258	—	—
5	0·282	100	107·2		0·282	—	—
6	0·332	80—100	110·7		0·261	0·071	—
7	0·118	100—116	114·0		0·064	0·054	—
8	0·038	110	115·5		0·016	0·022	—
9	0·134	Residue	133·3		—	0·024	0·110
Total	1·824			Total	1·543	0·171	0·110
				Ester, %	84·6	9·4	6·0
				Acid, %	84·3	9·5	6·2

(b) *Fractionation of methyl esters of water-insoluble dibasic acids* S_1.

No.	G.	Sap. equiv.		C_9	C_{11}	Dibasic esters: C_{13}	C_{15}	C_{15} Satd.
1	0·174	118·5		0·040	0·134	—	—	—
2	0·338	123·4		—	0·301	0·037	—	—
3	0·289	130·9		—	0·098	0·191	—	—
4	0·303	128·4		—	0·156	0·147	—	—
5	0·334	131·6		—	0·097	0·237	—	—
6	0·496	140·9		—	—	0·311	0·185	—
7	0·552	152·0		—	—	—	0·538	0·014
8	0·443	167·7		—	—	—	0·349	0·094
9	0·379	248·0		—	—	—	0·077	0·302
Total	3·308		Total	0·040	0·786	0·923	1·149	0·410
			Ester, %	1·2	23·8	27·9	34·7	13·6
			Acid, %	1·1	23·0	27·3	34·4	14·2

(c) *Combined results of ester fractionations.*

Dibasic acid	L_1 (32·9%)	S_1 (67·1%)	Total, %	Dibasic acids, % (mol.)
Azelaic acid	27·7	0·8	28·5	37·4
Undecanedioic	3·1	15·4	18·5	21·1
Tridecanedioic	2·1	18·3	20·4	20·6
Pentadecanedioic	—	23·1	23·1	20·9
C_{15}-satd.	—	9·5	9·5	—

Hydrogenation.—Methyl parinarate (44·3 g.) was hydrogenated at 100° with Raney nickel (*ca.* 2 g.) (Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471) in a three-necked 250-ml. round-bottomed flask, fitted with a mechanical stirrer (1300 r.p.m.) operating through a packed gland, and with a tube reaching to the bottom of the flask so that samples could be withdrawn without the hydrogenation being stopped. Before the experiment was begun, the apparatus was evacuated and filled with hydrogen; the progress of the reaction was followed by supplying the hydrogen to the reaction vessel from a graduated gas-container.

Examination of Hydrogenation Fractions.—Ozonolysis of fraction 2. The mixed acids (3·50 g.) from fraction 2 were dissolved in methyl acetate (40 ml.) and ozonised at −30°. The solvent was distilled off under reduced pressure, and the resultant ozonides were hydrolysed by refluxing them with water (100 ml.) for 90 minutes and then oxidised with 30% hydrogen peroxide (5 ml.) for 30 minutes. The cooled solution was filtered and the filtrate evaporated to dryness. The residue (0·28 g.) was twice recrystallised from ether and sublimed twice. The sublimate, m. p. 150—160°, was recrystallised from

water several times and yielded succinic acid (0·05 g.), m. p. 178—180° undepressed when admixed with authentic succinic acid (m. p. 182°).

Acetone–permanganate oxidation of fraction 3. Fraction 3 (13·18 g.) was oxidised in solution in acetone (140 ml.) with potassium permanganate (70 g.). There were recovered: unoxidised esters (methyl stearate) 0·47 g., I.V. 4·5; dibasic acids 6·46 g.; steam-volatile monobasic acids 1·99 g.

Examination of dibasic acids. The dibasic acids (6·46 g.) were separated by crystallisation from 400 ml. of water into two fractions; insoluble fraction S_1 4·30 g., soluble fraction L_1 2·11 g. Both fractions were esterified separately with methyl alcohol containing 0·5% of sulphuric acid and fractionated through a micro-fractionation column (Table IV).

Acetone–permanganate oxidation of fraction 5. Fraction 5 (14·05 g.) was oxidised in solution in acetone (140 ml.) with potassium permanganate (70 g.). There were recovered: methyl stearate 5·71 g., I.V. 1·0; dibasic acids 4·63 g.; and steam-volatile monobasic acids 2·20 g.

TABLE V.

Fractionation of the dimethyl esters of dibasic acids.

				Dibasic esters:			
No.		B.P./*ca.* 1 mm.	Sap. equiv.	C_9	C_{11}	C_{13}	C_{15}
1	0·453	<122°	116·7	0·159	0·294	—	—
2	0·532	122—130	117·8	0·146	0·386	—	—
3	0·584	130—140	119·2	0·106	0·478	—	—
4	0·534	140—130	122·5	—	0·513	0·021	—
5	0·461	130	126·2	—	0·312	0·149	—
6	0·699	140	132·2	—	0·175	0·524	—
7	0·257	140	137·7	—	—	0·223	0·034
8	0·123	140	141·8	—	—	0·069	0·054
9	0·134	140	143·4	—	—	0·060	0·074
10	0·073	140 Falling	143·5	—	—	0·032	0·041
11	0·258	Residue	157·5	—	—	—	0·258
Total	4·108		Total	0·511	2·158	1·078	0·461
			Ester, %	10·0	52·5	26·3	11·2
			Mol., %	11·7	54·4	24·5	9·4

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THE UNIVERSITY, LIVERPOOL. [*Received, May 15th,* 1951.]

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575. *The Mesomerism of Keten and Three of its Derivatives.*

By C. L. ANGYAL, G. A. BARCLAY, A. A. HUKINS, and R. J. W. LE FÈVRE.

The following apparent moments have been determined (refractivity method) in benzene: keten, 1·4$_8$; dimethylketen, 1·8$_7$; diphenylketen, 1·7$_6$; mesitylphenylketen, 1·7$_4$ D. Keten as a gas (temperature method) has—as predicted from $\mu_{C_6H_6}$ by the Barclay–Le Fèvre formulæ—a higher moment than that formerly quoted for it.

The polarities now found can be understood if the chief mesomeric displacements in ketens and ketones are opposite in character.

THAT a 1 : 2-dienoid system, X=Y=Z, having an unshared valency duplet in atoms X and/or Z, might exist in a mesomeric state, was first forecast by Ingold (*Chem. Reviews*, 1934, **15**, 225). The ketens were explicitly included as examples, since among them the terminal oxygens should allow the process, $R_2\overset{\curvearrowleft}{C}=C=\overset{\curvearrowleft}{O}$. At that time, the relevant evidence available was mainly of a qualitative kind, *e.g.*, that many (but not all; cf. Wilsmore and Deakin, *J.*, 1910, **97**, 1969; Gilman and Heckert, *J. Amer. Chem. Soc.*, 1920, **42**, 1010; Farmer and Farooq, *J.*, 1938, 1925) addition reactions proceeded as though the normal "carbonyl" activation, represented in ketones by $R_2C=\overset{\curvearrowright}{O}$, were developed less than another which polarised the C=C link (cf. Gilman, "Organic Chemistry," 2nd Edn., 1943, p. 1914).

Earlier physical work had not provided any unexpected information; thus Lardy (*J. Chim. physique*, 1924, **21**, 294; 353; cf. Henri, *Compt. rend.*, 1923, **177**, 1039) from the visible and ultra-violet spectra of keten and some substituted ketens had recognised only the presence of

bands usually found for molecules containing ketonic groups or olefinic double bonds, and von Auwers (*Ber.*, 1918, **51**, 1124) had observed the molecular refractions of diethyl- and diphenyl-keten to be approximately equal to the figures estimated by means of the usual atomic and group constants—an agreement predicted generally for 1 : 2-dienes by Brühl eleven years previously (*Ber.*, 1907, **40**, 1160).

However, in 1938 (*J. Chem. Physics*, **6**, 75), Beach and Stevenson published an electron-diffraction study of keten indicating that the distances C to C and C to O were 1·35 and 1·17 A. respectively, and that the C–C–O arrangement was linear. Since the corresponding dimensions

$CH_2{=}C{=}O$ (I.) $\quad \bar{C}H_2{-}C{\equiv}\overset{+}{O}$ (II.) $\quad R_2C{=}O$ (III.) $\quad R_2\overset{+}{C}{-}\bar{O}$ (IV.)

expected for (I) were 1·34 and 1·24 A., a 25% contribution from (II) was inferred. Recent spectroscopic data (Herzberg, quoted by Allen and Sutton, *Acta Cryst.*, 1950, **3**, 46) suggest a slightly greater variation from the " normal " interatomic separations, particularly for the C–O link, for which 1·102 A. is quoted. The Beach–Stevenson structure has been found compatible with the infra-red absorptions observed by Drayton and Thompson (*J.*, 1948, 1416), Halverson and Williams (*J. Chem. Physics*, 1947, **15**, 552), and Harp and Rasmussen (*ibid.*, p. 778).

Mesomeric polarisations of the type shown in the opening paragraph should be detectable by comparing the dipole moments of ketens and ketones, because for the latter an approximately equal contribution from the forms (III) and (IV) seems to be agreed (Pauling, " The Nature of the Chemical Bond," 2nd Edn., 1944, p. 75). In the two classes therefore the mesomeric moments will act in opposite directions, the effect of (IV) or (V) being to raise, and that of (II) to lower, the observable moment from a basic value which for both (I) and (III) should not be very different from that for formaldehyde, *i.e.*, 2·27 D. (Hurdis and Smyth, *J. Amer. Chem. Soc.*, 1943, **65**, 89). The discovery by Hannay and Smyth (*ibid.*, 1946, **68**, 1357) that the moment of keten, as a gas, appeared in fact to be much less than 2·27 D. was therefore of obvious significance. These authors, however, noted that if the real state of keten involves a 75% contribution of structures (I plus V) and 25% of (II) the molecular resultant should have its positive pole towards the oxygen atom, *i.e.*, the usual sense of ketonic polarity would be reversed. This conclusion was not pressed, and other contributory structures, such as (VI) and (VII), which tend to keep the oxygen negative, were mentioned.

$CH_2{=}\overset{+}{C}{-}\bar{O}$ (V.) $\quad \overset{+}{C}H_2{-}C{-}\bar{O}$ (VI.) $\quad \overset{+}{H}{\cdot}CH{\equiv}C{-}\bar{O}$ (VII.)

An alternative point of view has been argued by Walsh (*ibid.*, p. 2408) who explained the lowered carbonyl polarity in keten without recourse to resonance. The central C-atom is " acetylenic " or " digonal," forming two hybrid *s–p* bonds at 180°, and two π bonds having their central planes at right angles, thereby precluding conjugation and also reducing the C=O polarisation in keten relatively to that in, *e.g.*, formaldehyde.

Present Work.—The dipole moments of keten and its dimethyl, diphenyl, and mesitylphenyl derivatives have been determined in benzene solution. For other reasons (see later) the measurements of Hannay and Smyth on gaseous keten have been extended.

Results (refractivity method) are shown in Table I (top row).

Discussion.—The electrical effect of a methyl group on an attached olefinic link is to cause a small permanent polarity disposed in the direction to be expected if Me were " electron repelling." This action is quantitatively much the same in $Me{\cdot}CH{=}CH_2$ (μ = 0·35 D., McAlpine and Smyth, *ibid.*, 1933, **55**, 453; cf. Farmer and Warren, *J.*, 1933, 1297, 1302) as in toluene (μ = 0·37 D.; McAlpine and Smyth, *loc. cit.*). If therefore the observed moment of keten were caused by reversal of the normal carbonyl polarisation, the result of hydrogen replacement by methyl should be to make $\mu_{Me_2C{=}CO}$ *less* than $\mu_{CH_2{=}CO}$. Unfortunately the difficulties of handling dimethylketen in this work proved severe and, of many attempts, we only produced one solution of composition and purity on which we could depend. Its ε and d were therefore determined in triplicate, from which comes an estimated moment of $1{\cdot}8_7$ D. This is *greater* than $1{\cdot}4_2$, the figure for keten.

The increase of moment following dimethylation thus is about 0·4 D. for keten compared with *ca.* 0·6 D. for formaldehyde. Further, the moments of the four ketens are all smaller than those of the related ketones by amounts approximately 30—40% of μ_{ketone}; for the first two pairs these ratios are practically the same at 32% :

TABLE I.

	Parent.	Dimethyl-.	Diphenyl-.	Mesitylphenyl-.
Keten	$1{\cdot}4_3$	$1{\cdot}8_7$	$1{\cdot}7_6$	$1{\cdot}7_4$
Ketone	$2{\cdot}1_3$ *	$2{\cdot}7_4$	$2{\cdot}9_5$	$2{\cdot}6_5$
$\delta\mu$.....	$0{\cdot}6_9$	$0{\cdot}8_7$	$1{\cdot}1_9$	$0{\cdot}9_1$

* The data presented are measurements made in solution. Attempts to examine formaldehyde dissolved in benzene have been unsuccessful. From the molecular dimensions listed by Allen and Sutton (*Acta Cryst.*, 1950, **3**, 46) we find $A : B : C = 3{\cdot}80 : 3{\cdot}61 : 2{\cdot}90$, whence by eqn. (2) of *J.*, 1950, 3370, the required $(\mu_{CH_2O})_{C_6H_6}$ is calculable as $2{\cdot}1_3$ D. from $(\mu_{CH_2O})_{gas} = 2{\cdot}2_7$ D. We note that this result shows the polarity changes from formaldehyde to acetone not to be markedly affected by state: $(\mu_{Me_2CO})_{gas} = 2{\cdot}8_5$–$3{\cdot}0_3$, $(\mu_{Me_2CO})_{C_6H_6} = 2{\cdot}7_4$, $(\mu_{CH_2O})_{gas} = 2{\cdot}2_7$, estimated $(\mu_{CH_2O})_{C_6H_6} = 2{\cdot}1_3$ D.

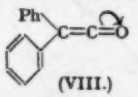
Attention may also be drawn to the alterations in moment, consequent on arylation, through the series:

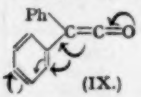
$$CH_2{:}C{:}O \longrightarrow CPh_2{:}C{:}O \quad (\delta\mu = 0{\cdot}3_3 \text{ D.}) \qquad \text{or} \qquad Ph{\cdot}C(C_6H_{11}){:}C{:}O \quad (\delta\mu = 0{\cdot}3_1 \text{ D.})$$

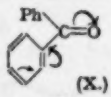
$$CH_2O \longrightarrow CPh_2{:}O \quad (\delta\mu = 0{\cdot}8_3 \text{ D.}) \qquad \text{or} \qquad Ph{\cdot}C(C_6H_{11}){:}O \quad (\delta\mu = 0{\cdot}5_3 \text{ D.})$$

Replacement of phenyl by mesityl affects the ketones more than the ketens.

From what has been said earlier it is evident that in $CPh_2{:}C{:}O$ and $CPh_2{:}O$ major mesomeric polarisations, of the types exemplified by (VIII), (IX), and (X), may be expected:


(VIII.)


(IX.)


(X.)

The last two will create, in the real structures of such molecules, a tendency for the diarylmethylene portions to become planar. The Ph–C–Ph angle in diphenylmethane or 1 : 1-diphenyl*cyclo*propane seems to be about 116° (Goldsmith and Wheland, *J. Amer. Chem. Soc.*, 1948, **70**, 2632), but when there is resonance—as in 1 : 1-diphenylethylene—this angle is increased to 125° (Coates and Sutton, *J.*, 1942, 567), although even so a 30° twist of the phenyl groups out of the common plane is necessary to provide the minimum permissible distance of 2·4 A. between unbonded hydrogen atoms. Accordingly, when in (IX) and (X), a phenyl is replaced by the bulkier mesityl, the steric inhibition of resonance (cf. Birtles and Hampson, *J.*, 1937, 10; Ingham and Hampson, *J.*, 1939, 981) should be aggravated. Consistently with this, the moment of mesityl phenyl ketone ($2{\cdot}6_3$ D.) is smaller than that of benzophenone ($2{\cdot}9_5$ D.). The moments of the two arylketens are, however, the same—from which fact we infer that the spatial requirements of the aryl groups influence the mesomeric state less than they do with the ketones. Moreover, polarisations of type (VIII) cannot be transmitted by the usual duplet transfer mechanisms into the phenyl groups. We conclude therefore that forms such as (IX)—namely those conferring a partial double-bond character on the Ar–C links—are evidently not predominant contributors with diphenylketen.

We submit therefore that our measurements can be most readily interpreted if in ketens the mesomerism expressed by is reduced but not extinguished by competition with other displacements, such as , which are not probable with ordinary aldehydes or ketones.

Dependence of the Apparent Dipole Moment of Keten on the Solvent.—In a previous paper (*J.*, 1950, 3370) we have examined three equations whereby the ratio $\mu_{solution}/\mu_{gas}$ may be predicted. One of these requires knowledge of the refractive index of the solute at the temperature of comparison (25°) and is therefore inapplicable in the present case. There remain however (*A*) and (*B*):

$$\mu_s^2/\mu_v^2 = 1 + f(\varepsilon)[\text{Exp } x^2 - \text{Exp } (h_2^2 - h_1^2)] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

$$\mu_s^2/\mu_v^2 = 1 + f(\varepsilon)\{\text{Exp } x^2 - \text{Exp } [(R_1/R_2)(1 - A_1B_1C_1/A_2B_2C_2)]\} \quad . \quad . \quad . \quad . \quad (B)$$

The symbols are explained in the reference cited. For brevity we here write $f(\varepsilon)$ for the volume polarisation of the solvent, taking it as 0·2962 for benzene at 30°. In addition, $h_2^2 = 0{\cdot}101$, $R_2 = 26{\cdot}15$ c.c., and $A_2B_2C_2 = 117{\cdot}6$ (Holland and Le Fèvre, *J.*, 1950, 2166). From the scale drawing (Fig. 1; cf. Allen and Sutton, *loc. cit.*) the dimensions A_1, B_1, and C_1 are seen to be 5·19, 3·65, and 2·90 respectively.

Substitution, etc., gives from (*A*): $\mu_{gas} = 1{\cdot}091\mu_{C_6H_6}$ and from (*B*): $\mu_{gas} = 1{\cdot}134\mu_{C_6H_6}$

Since the moment now found in benzene is 1·43 D. our predictions of μ_{gas} [from (*A*), 1·56; from (*B*), 1·62 D.] are higher than the figure (1·45 D.) quoted from experiment by Hannay and Smyth (*loc. cit.*). These authors had listed polarisations at four temperatures between 397·8° and 446·3° K. inclusive, and we noticed that—*via* least squares—their data fitted the relation: $P = 5{\cdot}62 + 15031/T$, whence $\mu = 1{\cdot}57$ D. The matter was discussed in correspondence with Professor Smyth, who rightly commented that the temperature range covered in his determinations with Hannay was too short to justify the deduction of constants for the Debye equation. Accordingly we undertook additional measurements at three points below 398° K., thus providing the extension illustrated in Fig. 2 (total polarisation plotted against $1/T$).

It is seen that all seven points can be fairly represented by a single line, the (calculated) equation to which is: $P = 7{\cdot}97 + 14080/T$, whence $\mu = 1{\cdot}52$ D. Although this is smaller than either of the predicted values of μ_{gas}, it is nearer to that (1·56 D.) required by (*A*) than to

FIG. 1.

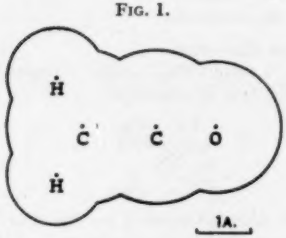
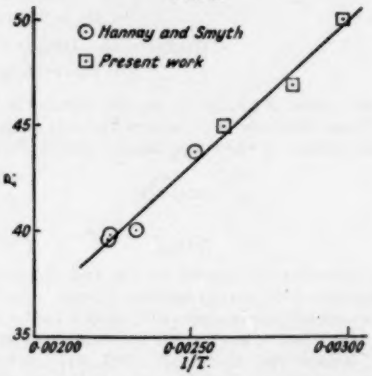


FIG. 2.



that required by (*B*). Such a relative applicability of the two expressions is in accord with our earlier conclusions (*J.*, 1950, 3370).

In previous papers, whenever a distortion polarisation ($_DP$) has seemed dependable, we have estimated μ_a^2/μ_g^2 directly as a ratio of orientation polarisations, *i.e.*, as $(\infty P_a - {}_DP)/(P_g - {}_DP)$. Yet in view of the refractometric evidence from substituted ketens (cf. von Auwers and Brühl, *loc. cit.*) and because the calculated $(R_L)_D$ for keten is 11·0 c.c., we suspect that 7·97 c.c. is too low for the $_DP$ of this molecule. In general, $_DP$ is difficult to fix accurately from polarisation–temperature measurements, and for a given substance may vary according to the observer without greatly affecting the values for μ_{gas} also produced (cf. *J.*, 1950, 561, for an example), the latter depending only on the slope—not the height—of the P versus $1/T$ curve. In the present case therefore we have compared μ_a, obtained *via* a $_DP$ of 11·0 c.c., with μ_g estimated from the inclination of the best fitting straight line through the seven points shown in Fig. 2.

EXPERIMENTAL.

Keten.—This was obtained from acetone in a "lamp" of the type described by Williams and Hurd (*J. Org. Chem.*, 1940, **5**, 122) and purified by the method of Rice, Greenberg, Waters, and Vollrath (*J. Amer. Chem. Soc.*, 1934, **56**, 1760). It was admitted to the dielectric constant apparatus at *E* of Fig. 2 of *J.*, 1950, 278, and redistilled into trap *D* immediately before measurement.

Dimethylketen.—Owing to the rapidity with which this substance reacted with atmospheric moisture, we eventually attempted to make only one solution straight away from each high-vacuum decomposition of dimethylmalonic anhydride (Staudinger, *Helv. Chim. Acta*, 1925, **8**, 306, cf. Adams *et al.*, "Organic Reactions," 1946, Vol. III, p. 135). The crude condensates were redistilled under oxygen-free nitrogen and collected (b. p. 34°/760 mm.) in a liquid-air trap, from which absorption into a known weight of benzene was induced as described for sulphur dioxide (*J.*, 1950, 283).

Diphenylketen.—This was prepared from benzil monohydrazone and "azibenzil" (Schroeter, *Ber.*, 1909, **42**, 2336; Staudinger, *ibid.*, 1911, **44**, 1619) by thermal decomposition of the latter, followed by a final distillation immediately before admixture with benzene. All operations were as far as possible conducted in oxygen-free nitrogen. The three solutions (denoted by X, Y, and Z) for which data are tabulated below each contained the total material from a separate preparation, the solute in X having b. p. 85—88 at *ca.* 0·1 mm., those in Y and Z, b. p. 100°/0·2 mm.

At first we obtained poor results for the mercuric oxide oxidation of the hydrazone, but ultimately

it appeared that *freshly prepared* oxide behaved satisfactorily if used at once. This is in agreement with findings by Ritter and Wiedemann (*J. Amer. Chem. Soc.*, 1929, **51**, 3583) but is in contradiction to those by Taylor *et al.* (*J.*, 1938, 206) who advise that the oxide be given a preliminary exposure for 24 hours to the moist air of the laboratory.

Mesitylphenylketen.—The thermal decomposition of mesitylphenylacetyl chloride (from mesitylene and mandelic acid with anhydrous stannic chloride), by the procedure of Fuson, Armstrong, Kneisley, and Shenk (*J. Amer. Chem. Soc.*, 1944, **66**, 1464), gave a yellow liquid, b. p. 182—185°/21 mm., from which a fraction of b. p. 108°/0·2 mm. was selected for the present work.

Dimeric Ethylcarbethoxyketen.—For both the preparation of α-bromo-α-carbethoxybutyryl chloride, and its reaction with zinc filings, the directions of Staudinger and St. Bereza (*Ber.*, 1909, **42**, 4908) were followed, a colourless liquid with a faint ether-like odour, b. p. 89°/0·07 mm., resulting. Staudinger had reported the dimer as boiling at 113—116° under " absolute vacuum; " since our product also had b. p. 100°/0·3 mm., it seemed possible that it was in fact the dimer. Analysis showed a high hydrogen content (Found: C, 59·1; H, 8·2. Calc. for $C_8H_{16}O_3$: C, 59·1; H, 7·0%). Prolonged heating (5 hours) of this substance at 200—220°/*ca.* 20 mm. caused only partial decomposition and did not produce any of the monomer.

Mesityl Phenyl Ketone.—We are indebted to Mr. D. R. Penman for a specimen of this substance (Louise, *Ann. Chim. Physique*, 1885, **6**, 202; Elbs, *J. prakt. Chem.*, 1887, **35**, 486), b. p. 169—175°/2 mm.

Measurements.—The three new determinations of the polarity of keten as a gas have been made with apparatus similar to that described before (*J.*, 1950, 290). The quantities in the third column of Table II are computed relatively to the temperature-invariant total polarisation of carbon dioxide (*viz.*, 7·341 c.c., cf. *Trans. Faraday Soc.*, 1947, **43**, 374) by the expression: $P_{keten} = 7{\cdot}341\ (\delta C/p)^{Keten}_{p\to 0}/(\delta C/p)^{CO_2}_{p\to 0}$. The standardising equation required was found by measurement to be: $(\delta C/p)^{CO_2}_{p\to 0} = 2307{\cdot}4/T - 0{\cdot}054$.

TABLE II.

Polarisations of gaseous keten.

T (° K.).	$(\delta C/p)_{p\to 0}$.	P (c.c.).	P (calc.).	p range (cm. Hg).	No. of observations.
335·5°	46·64	50·17	49·93	20—65	11
355·0	41·26	46·99	47·63	27—68	13
384·0	36·48	44·98	44·63	25—65	11

The following data refer to solutions in sodium-dried benzene; methods, symbols, and calculations are explained in *J.*, 1937, 1805; 1948, 1949; 1949, 333; *Trans. Faraday Soc.*, 1950, **46**, 1. Unfortunately certain of our observations were made at seasons when room temperatures were above 25°. Appropriate values of p_2 and C from Table III for use in Table IV are:

Temp.	25°	27°	30°
p_2	0·3409	0·3410	0·3416
C	0·1881	0·1889	0·1904

TABLE III.

Dielectric constants and densities of solutions.

Keten.

10^4w_1.	ε^{20}.	$\alpha\varepsilon_2$.	d_4^{20}.	βd_2.
0	2·2628	—	0·86718	—
4,085	2·2821	4·72	0·86689	−0·071
5,902	2·2876	4·20	0·86853	−0·110
6,943	2·2932	4·39	0·86656	−0·089
9,530	—	—	0·86598	−0·126
12,840	2·3218	4·60	0·86585	−0·103
13,510	2·3230	4·46	0·86605	−0·084
13,940	—	—	0·86586	−0·095
19,050	2·3548	4·83	0·86493	−0·118
19,540	2·3567	4·81	0·86496	−0·114
28,160	—	—	0·86430	−0·102

whence mean $\alpha\varepsilon_2 = 4{\cdot}57$, mean $\beta d_2 = -0{\cdot}101$.

Dimethylketen.

10^4w_1.	ε^{27}.	$\alpha\varepsilon_2$.	d_4^{27}.	βd_2.
0	2·2687	—	0·87168	—
9,249	2·3159	5·10	0·87174	0·006

Diphenylketen.

10^4w_1.	ε^{25}.	$\alpha\varepsilon_2$.	d_4^{25}.	βd_2.	n_D^{25}.
0	2·2725	—	0·87378	—	1·4982
(*X*) 9,099	2·2930	2·25	0·87551	0·190	—
(*Y*) 14,963	2·3086	2·41	0·87679	0·201	1·4998
(*Z*) 16,284	2·3133	2·51	0·87734	0·219	—

whence $(\alpha\varepsilon_2)_{w_1} = 1{\cdot}94 + 33\ w_1$; $(\beta d_2)_{w_1} = 0{\cdot}158 + 3{\cdot}4w_1$.

Mesitylphenylketen.

10^4w_1.	ε^{25}.	$\alpha\varepsilon_2$.	d_4^{25}.	βd_2.	n_D^{25}.
0	2·2715	—	0·87378	—	1·5001
8,484	—	—	0·87522	0·170	1·5007
0	2·2628	—	0·86718	—	Temp. = 30°
10,705	2·2788	1·49$_5$	0·86880	0·151	
17,791	2·2890	1·47	0·86987	0·151	
24,797	2·3001	1·50	0·87091	0·150	
37,684	2·3217	1·56	0·87290	0·152	

Mesityl phenyl ketone.

10^4w_1.	ε^{25}.	$\alpha\varepsilon_2$.	d_4^{25}.	βd_2.
0	2·2725	0 —	0·87378	—
12,809	2·3184	3·58	0·87602	0·175
18,908	2·3400	3·57	0·87676	0·153
25,492	2·3637	3·58	0·87789	0·161
31,221	2·3847	3·59	0·87877	0·160

whence mean $\alpha\varepsilon_2 = 3{\cdot}58$; mean $\beta d_2 = 0{\cdot}162$.

Dimeric carbethoxyethylketen.

10^4w_1.	ε^{25}.	$\alpha\varepsilon_2$.	d_4^{25}.	βd_2.
0	2·2725	—	0·87378	—
16,399·5	2·3594	5·30	0·87618	0·146

TABLE IV.

Calculation of results.

Solute.	Mol. wt.	α_{Li}.	β.	${}_{\infty}P_1$ (c.c.).	T.	$(R_L)_D$ (c.c.).	μ (D.).
Keten	42·0	4·57	−0·116	52·6	30°	11·0 *	$1{\cdot}4_3$
Dimethylketen	70·1	5·10	0·007	91·3	27°	20·2 *	$1{\cdot}8_7$
Diphenylketen	194·2	1·94	0·181	125·1	25°	62·0	$1{\cdot}7_6$
Mesitylphenylketen	236·3	1·51	0·174	134·6	30°	73·5	$1{\cdot}7_4$
Mesityl phenyl ketone	224·3	3·58	0·185	213·4	25°	69·1	$2{\cdot}6_5$
Supposed dimeric ethylcarbethoxyketen	284·3	5·30	0·167	364·1	25°	68	$3{\cdot}8_0$

* Calc. from constants given in Landolt–Börnstein, " Tabellen," 4th Edn., p. 1039.

A preliminary statement (Hukins and Le Fèvre, *Nature*, 1949, **164**, 1050) on the present work gave certain figures which should now be replaced by these in Table IV.

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576. *The Search for Chemotherapeutic Amidines. Part XI.* Phenanthridines. Part II.*

By D. D. LIBMAN and R. SLACK.

Derivatives of 9-phenylphenanthridine have been prepared and examined for trypanocidal activity.

SEVERAL years ago, stimulated by the work of Walls (*J.*, 1938, 389; 1945, 294), Barber, Gregory, Major, Slack, and Woolman (*J.*, 1947, 84) examined amidine analogues of 9-*p*-amidinophenyl-7-amino-10-methylphenanthridinium chloride (" Phenidium Chloride "). Although no pronounced trypanocidal activity was found, we have since modified 2 : 7-diamino-10-methyl-9-phenylphenanthridinium chloride (" Dimidium Chloride "; Walls, 1945, *loc. cit.*), another active trypanocide, in a similar manner and have prepared 2 : 7-diamidino-9-phenylphenanthridine dihydrochloride (I) and 2 : 7-diamidino-10-methyl-9-phenylphenanthridinium chloride dihydrochloride (II), both of which are slightly trypanocidal. Replacement of the 2 : 7-diamino-groups of 2 : 7-diamino-9-*p*-aminophenyl-10-methylphenanthridinium chloride (Walls and Whittaker, *J.*, 1950, 41) by halogen atoms also has a dystherapeutic effect and 2 : 7-dichloro-9-*p*-aminophenylphenanthridine (III) exhibits only slight biological activity. 2 : 7-Dibromo-9-*p*-nitrophenylphenanthridine and the corresponding methobisulphate have also been prepared.

2 : 7-Dicyano-9-phenylphenanthridine was obtained from the corresponding diamine (Walls, *J.*, 1945, 294) by the normal Sandmeyer procedure and gave a di-imino-ether hydrochloride on prolonged treatment with alcohol and dry hydrogen chloride. Reaction with saturated alcoholic ammonia gave the required diamidine dihydrochloride. With methyl sulphate in nitrobenzene, the dinitrile gave the corresponding methosulphate which was converted *in situ* into the methochloride. It was difficult to achieve satisfactory combustion analyses of this quaternary salt despite rigorous purification (cf. Barber *et al.*, *loc. cit.*). However, conversion into 2 : 7-diamidino-10-methyl-9-phenylphenanthridinium chloride dihydrochloride proceeded smoothly through the di-imino-ether.

p-Nitrobenzoyl chloride and 2-amino-4 : 4′-dibromodiphenyl in pyridine gave 4 : 4′-dibromo-2-*p*-nitrobenzamidodiphenyl in excellent yield, and very smooth ring closure to 2 : 7-dibromo-9-*p*-nitrophenylphenanthridine was accomplished by phosphorus oxychloride in nitrobenzene. Quaternation with methyl sulphate proceeded normally, the product being conveniently isolated as the hydrogen sulphate.

2 : 7-Dichloro-10-methyl-9-*p*-nitrophenylphenanthridinium methosulphate was obtained by a similar sequence of reactions and was reduced with iron and acetic acid to the corresponding amine, 9-*p*-aminophenyl-2 : 7-dichloro-10-methylphenanthridium chloride.

EXPERIMENTAL.

2 : 7-*Dicyano*-9-*phenylphenanthridine* [with Mrs. P. Z. SLACK, *née* Gregory].—2 : 7-Diamino-9-phenylphenanthridine (8·0 g.) in concentrated hydrochloric acid (18 c.c.) and water (50 c.c.) was

* Part X, *J.*, 1949, 642. Part V (Phenanthridines. Part I), *J.*, 1947, 84.

tetrazotised at 0° with sodium nitrite (4·2 g.) in a little water. After neutralisation (sodium carbonate), the dark solution was poured, with stirring, into a solution of potassium cyanide (9·5 g.) and cuprous cyanide (6·3 g.) in water (25 c.c.). After being heated at 100° for 2 hours, the crude product was collected and washed with hot potassium cyanide solution, followed by boiling water. Sublimation at 0·1 mm./300° gave the yellow crystalline *dinitrile* (1·8 g.), m. p. 302° after recrystallisation from pyridine or anisole (Found: C, 82·9; H, 3·9; N, 13·5. $C_{21}H_{11}N_3$ requires C, 82·7; H, 3·6; N, 13·8%).

2 : 7-*Diamidino*-9-*phenylphenanthridine Dihydrochloride*.—The above dinitrile (0·75 g.) in absolute alcohol (15 c.c.) was saturated with dry hydrogen chloride at 0°, and the tube sealed and kept at room temperature for 3 weeks. The solid was collected, washed with dry ether, and treated with saturated alcoholic ammonia solution (25 c.c.) at 40—50° for 36 hours. After filtration, the solution was cooled very slowly, the *diamidine dihydrochloride* separating over a long period in beautiful pale-green rosettes. Recrystallisation from alcohol–ether (ice-box) gave the *monoalcoholate* (0·25 g.), m. p. (decomp.) 265—267° (Found: N, 15·8; Cl, 15·6; $C_{21}H_{19}N_5Cl_2,C_2H_5{\cdot}OH$ requires N, 15·35; Cl, 15·6%).

2 : 7-*Dicyano*-10-*methyl*-9-*phenylphenanthridinium Chloride*.—2 : 7-Dicyano-9-phenylphenanthridine (5·9 g.), dry nitrobenzene (50 c.c.), and methyl sulphate (4 c.c.) were gently refluxed for 5 minutes. The dark solution was cooled and shaken with ether (100 c.c.) and water (60 c.c.). The aqueous layer was separated and evaporated to half its volume. Ammonium chloride was added, and the precipitated *chloride* was crystallised from a little water, forming reddish needles, m. p. (decomp.) 300° (39%) (Found: N, 10·8; Cl, 10·9. $C_{23}H_{14}N_3Cl$ requires N, 11·8; Cl, 10·0%).

2 : 7-*Diamidino*-10-*methyl*-9-*phenylphenanthridinium Chloride Dihydrochloride*.—The above nitrile (510 mg.) was suspended in dry ethanol (10 c.c.) and saturated at 0° with dry hydrogen chloride. The mixture was kept for 2 days and diluted with dry ether. The precipitate was washed with dry ether and redissolved in saturated alcoholic ammonia (25 c.c.). After 15 hours at room temperature the solution was warmed to 40—50° for 1½ hours and evaporated to dryness at this temperature *in vacuo*. The residue was dissolved in water (5 c.c.) containing a little hydrochloric acid and reprecipitated by dropwise addition of acetone (30 c.c.). The high-melting *salt* (69%) formed needles from 4N-hydrochloric acid (Found: N, 12·6; Cl, 19·7. $C_{23}H_{22}N_5Cl_3,5H_2O$ requires N, 12·7; Cl, 19·3%).

2-*Amino*-4 : 4′-*dibromodiphenyl*.—This was prepared in 63% yield from the nitro-compound by Ritchie (*J. Proc. Roy. Soc. N.S.W.*, 1945, **78**, 141) by use of stannous chloride in ethanol. The following procedure was found more convenient. 4 : 4′-Dibromo-2-nitrodiphenyl (35·7 g.) was dissolved in boiling acetic acid (90 c.c.) and water (10 c.c.). Reduced iron powder (30 g.) was added at such a rate (during about 20 minutes) as to keep the mixture boiling vigorously; 80% acetic acid (40 c.c.) was added to replace evaporation losses. The mixture was heated for 30 minutes on the steam-bath, diluted with water (500 c.c.), and filtered. The solid was washed well with water and extracted with ether. The solution was dried and evaporated, giving a nearly colourless product (99%), m. p. 120°. This was pure enough for the next stage, but could be recrystallised from methanol to give pure material, m. p. 130°.

4 : 4′-*Dibromo*-2-p-*nitrobenzamidodiphenyl*.—A mixture of the above amine (3·27 g.), *p*-nitrobenzoyl chloride (2·0 g.), and dry pyridine (5 c.c.) was warmed for 75 minutes on the steam-bath and poured into 2N-hydrochloric acid (50 c.c.). The dark oil readily solidified and was washed with water and alcohol. The *benzoyl* compound (95%) crystallised from nitromethane as bright yellow needles, m. p. 203° (Found: N, 6·2; Br, 33·6. $C_{19}H_{12}O_3N_2Br_2$ requires N, 5·9; Br, 33·6%).

2 : 7-*Dibromo*-9-p-*nitrophenylphenanthridine*.—The above amide (2·8 g.), nitrobenzene (9 c.c.), and phosphorus oxychloride (4·5 c.c.) were refluxed for 6 hours in an oil-bath at 185°. The mixture was cooled, decomposed with ice, cautiously basified with concentrated aqueous ammonia, and steam-distilled. The residual solid was collected, and washed with water, alcohol, and ether. The *phenanthridine* (97%) formed khaki-coloured needles, m. p. 255°, from nitroethane (Found: N, 6·2; Br, 33·6. $C_{19}H_{10}O_2N_2Br_2$ requires N, 6·1; Br, 34·9%).

2 : 7-*Dibromo*-10-*methyl*-9-p-*nitrophenylphenanthridinium Hydrogen Sulphate*.—The above phenanthridine (1 g.) was heated for 15 minutes with gently refluxing nitrobenzene (10 c.c.) and methyl sulphate (0·5 c.c.). The solution was steam-distilled until all nitrobenzene had been removed, and the hot aqueous solution was decanted from tar. The yellow solid obtained after cooling was recrystallised from dilute sulphuric acid to give the *hydrogen sulphate* (33%), m. p. 226° (Found: N, 4·9; Br, 28·5. $C_{20}H_{12}O_2N_2Br_2,H_2SO_4$ requires N, 4·9; Br, 28·1%).

2-Amino-4 : 4′-dichlorodiphenyl is described by Monsanto and Jenkins (U.S.P. 2,084,033/1936), who reduced the nitro-compound with iron and hydrochloric acid. Using the method described for the bromo-analogue (above) we obtained an 84% yield of material having m. p. 91°. 4 : 4′-*Dichloro*-2-p-*nitrobenzamidodiphenyl*, prepared in 85% yield by the method described for the bromo-compound, crystallised from nitromethane in yellow needles, m. p. 203° (Found: N, 7·5. $C_{19}H_{12}O_3N_2Cl_2$ requires N, 7·2%).

2 : 7-*Dichloro*-9-p-*nitrophenylphenanthridine*.—The amide was cyclised as in the case of the bromo-phenanthridine, rather longer heating being required. The *phenanthridine*, which crystallised from nitromethane in pale yellow fluffy needles, m. p. 250°, was obtained in 70% yield, a small amount of unchanged amide being recovered (Found: N, 7·6; Cl, 19·0. $C_{19}H_{10}O_2N_2Cl_2$ requires N, 7·7; Cl, 19·2%).

2 : 7-*Dichloro*-10-*methyl*-9-p-*nitrophenylphenanthridinium Methosulphate*.—The phenanthridine (1 g.) was converted as above into the yellow *methosulphate* (92%), m. p. 320° (decomp.), after being washed with water, alcohol, and ether. It was insoluble in alcohol, water, acetic acid, nitrobenzene, and Cellosolve, and could not be further purified (Found: N, 5·7; Cl, 14·2. $C_{20}H_{12}O_2N_2Cl_2,CH_3{\cdot}HSO_4$ requires N, 5·7; Cl, 14·4%).

9-p-*Aminophenyl*-2 : 7-*dichloro*-10-*methylphenanthridinium Chloride*.—The nitro-compound (1 g.) and

iron dust (1 g.) in 90% acetic acid (10 c.c.) were refluxed for 1 hour, after which the mixture was diluted with water and filtered. The filtrate was concentrated, treated with water, evaporated to low bulk, and redissolved in water (40 c.c.). This solution was then filtered and treated with ammonium chloride. The precipitated *chloride* was recrystallised from water, giving dull crimson prisms (95%), m. p. 216° (Found: C, 58·6; H, 4·6; N, 6·8; Cl, 24·9; 25·3. $C_{20}H_{14}N_8Cl_2.H_2O$ requires C, 58·9; H, 4·2; N, 6·9; Cl, 26·1%).

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577. *The Nitration of 6-Hydroxynicotinic Acid and Related Compounds.*

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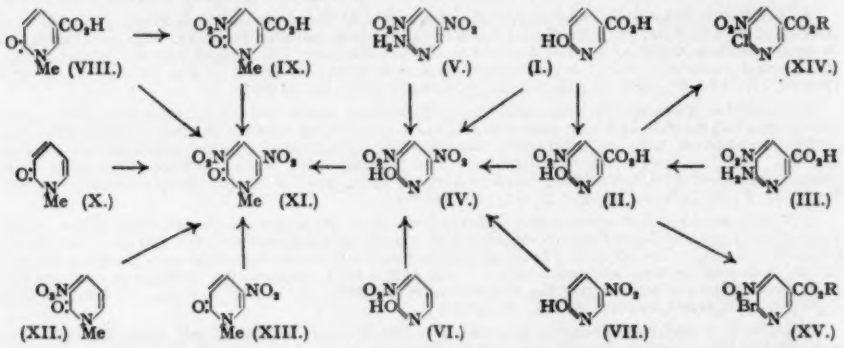
Nitration of 6-hydroxynicotinic acid gives 6-hydroxy-5-nitronicotinic acid and then 3 : 5-dinitro-2-pyridone. Similarly nitration of 1 : 6-dihydro-6-keto-1-methylnicotinic acid gives 1 : 6-dihydro-6-keto-1-methyl-5-nitronicotinic acid and finally 1-methyl-3 : 5-dinitro-2-pyridone.

THIS paper describes the preparation of a number of pyridine intermediates some of which are required in a projected synthesis of lysergic acid.

Nitration of 6-hydroxynicotinic acid (I) gives two products according to the reaction conditions. Treatment of (I) with fuming nitric acid at 50° gives 6-hydroxy-5-nitronicotinic acid (II) identical with that prepared by Räth and Prange (*Annalen*, 1928, **467**, 1) by the action of alkali on 6-amino-5-nitronicotinic acid (III). The acid (II) has been characterised by the formation of the methyl and the ethyl ester.



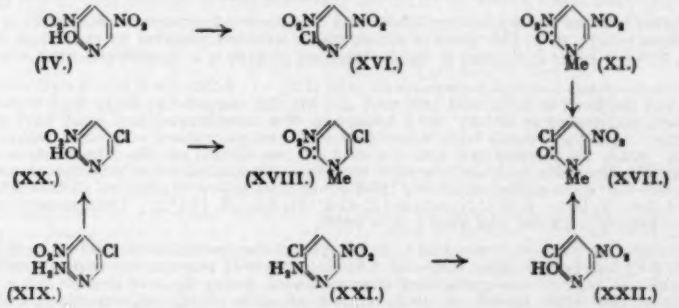
When heated under reflux with fuming nitric acid, 6-hydroxynicotinic acid gives a dinitropyridone, m. p. 175°, which is also obtained by similar treatment of 6-hydroxy-5-nitronicotinic acid. The compound, m. p. 175°, has been identified as 3 : 5-dinitro-2-pyridone (IV) by its preparation from 2-amino-3 : 5-dinitropyridine (V) (Tschitschibabin and Rasorenow, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1286; Tschitschibabin and Kirssanow, *Ber.*, 1928, **61**, 1223) by treatment with nitrous acid, and by its formation by nitration of either 3-nitro-2-pyridone (VI) or 5-nitro-2-pyridone (VII) (Tschitschibabin and Bylinkin, *J. Russ. Phys. Chem. Soc.*, 1918, **50**, 471; Tschitschibabin, *ibid.*, 1914, **46**, 1236).

A further proof of the structure ascribed to the dinitration product from 6-hydroxynicotinic acid has been obtained by a study of the nitration of 1 : 6-dihydro-6-keto-1-methylnicotinic acid (VIII). Treatment of this acid with fuming nitric acid at 55° gives 1 : 6-dihydro-6-keto-1-methyl-5-nitronicotinic acid (IX) characterised by the formation of the methyl and the ethyl ester. When 1 : 6-dihydro-6-ketonicotinic acid is heated under reflux with fuming nitric

acid it gives a methyldinitropyridone, m. p. 178°, which is also obtained by similar treatment of 1 : 6-dihydro-6-keto-1-methyl-5-nitronicotinic acid. The compound, m. p. 178°, which is identical with the product obtained by Fischer and Chur (*J. prakt. Chem.*, 1916, [2], **93**, 363) from the nitration of 1-methyl-2-pyridone (X), has been identified as 1-methyl-3 : 5-dinitro-2-pyridone (XI) by its formation from 1-methyl-3-nitro-2-pyridone (XII) (Tschitschibabin and Konowalowa, *Ber.*, 1925, **58**, 1712) and 1-methyl-5-nitro-2-pyridone (XIII) (Räth, *Annalen*, 1930, **484**, 52) on nitration. Methylation of the dinitration product from 6-hydroxynicotinic acid gives 1-methyl-3 : 5-dinitro-2-pyridone, thus confirming the structure (IV) ascribed to the former compound.

The structure ascribed to 1 : 6-dihydro-6-keto-1-methyl-5-nitronicotinic acid (IX) depends on its formation from 1 : 6-dihydro-6-keto-1-methylnicotinic acid and on its conversion into 1-methyl-3 : 5-dinitro-2-pyridone. Other attempts to correlate it with compounds of established structure were not successful. Thus 6-hydroxy-5-nitronicotinic acid (II) was recovered unchanged after attempted methylation with either methyl iodide or methyl sulphate, and attempts to convert (IX) into the ester of 6-chloro- (XIV) or 6-bromo- (XV) -5-nitronicotinic acids, by treatment with phosphoryl chloride–phosphorus pentachloride or phosphorus tribromide–pentabromide followed by treatment of the products with alcohol, were unsuccessful, although (XIV, R = Me and Et) and (XV, R = Me and Et) were readily obtained by similar treatment of 6-hydroxy-5-nitronicotinic acid (II).

An attempt to confirm the relationship of 3 : 5-dinitro-2-pyridone (IV) and 1-methyl-3 : 5-dinitro-2-pyridone (XI) by the conversion of each into 2-chloro-3 : 5-dinitropyridine was not successful. Reaction of 3 : 5-dinitro-2-pyridone with phosphoryl chloride–phosphorus pentachloride proceeds smoothly to give 2-chloro-3 : 5-dinitropyridine (XVI). Treatment of 1-methyl-3 : 5-dinitro-2-pyridone (XI) with phosphoryl chloride–phosphorus pentachloride gives a compound, $C_6H_2O_3N_3Cl$, m. p. 115°, formed by the replacement of a nitro-group in (XI) by chlorine; this compound can be obtained in better yield by treatment of (XI) with thionyl chloride. The compound, m. p. 115°, has been shown by synthesis to be 3-chloro-1-methyl-5-nitro-2-pyridone (XVII) and to be different from 5-chloro-1-methyl-3-nitro-2-pyridone (XVIII). The last compound has been synthesised by the following route. Treatment of 2-amino-5-chloro-3-nitropyridine (XIX) (Tschitschibabin and Jegorow, *J. Russ. Phys. Chem. Soc.*, 1928, **60**, 683; Tschitschibabin and Kirssanow, *Ber.*, 1927, **60**, 766) with nitrous acid gives 5-chloro-3-nitro-2-pyridone (XX), methylation of which yields the required 5-chloro-1-methyl-3-nitro-2-pyridone (XVIII) which is distinct from the product obtained by chlorination of 1-methyl-3 : 5-dinitro-2-pyridone.



The synthesis of (XVII) was effected by treatment of 2-amino-3-chloro-5-nitropyridine (XXI) (Bystritskaya and Kirssanow, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 1827) with nitrous acid to give 3-chloro-5-nitro-2-pyridone (XXII), methylation of which gives the required 3-chloro-1-methyl-5-nitro-2-pyridone, identical with the product obtained by chlorination of 1-methyl-3 : 5-dinitro-2-pyridone.

The detailed proof of the structure of the dinitropyridone obtained from 6-hydroxynicotinic acid as described above is necessary since Tschitschibabin and Schapiro (*J. Russ. Phys. Chem. Soc.*, 1921, **53**, 233; cf. Binz and Maier-Bode, *Angew. Chem.*, 1936, **49**, 486) have claimed that nitration of 2-pyridone gives a product, m. p. 286° (decomp.), described as 3 : 5-dinitro-2-pyridone, the properties of which are entirely different from those of the 3 : 5-dinitro-2-pyridone

described above. We have repeated the nitration of 2-pyridone according to Tschitschibabin and Schapiro and have obtained a product which has the properties of the compound described by these authors. We believe that the compound, m. p. 286° (decomp.), is a mixture of the sodium salt of 3-nitro-2-pyridone and the sodium salt of 3 : 5-dinitro-2-pyridone. Further nitration of the compound, m. p. 286° (decomp.), gives 3 : 5-dinitro-2-pyridone, m. p. 175°, in good yield.

Experimental.

6-Hydroxy-5-nitronicotinic Acid (II).—A solution of 6-hydroxynicotinic acid (50 g.) in nitric acid (500 c.c.; *d* 1·52) was kept at 45—50° for 4 hours. The mixture was evaporated under reduced pressure and the residue crystallised from water, giving 6-hydroxy-5-nitronicotinic acid (20 g.) as yellow needles, m. p. 278° (decomp.) undepressed by a specimen, m. p. 279—280° (decomp.), prepared as described by Rath and Prange (*loc. cit.*) (Found: C, 39·1; H, 2·3; N, 15·2. Calc. for $C_6H_4O_5N_2$: C, 39·1; H, 2·2; N, 15·2%). Light absorption in water: Maxima at 2110 (ε = 19,200) and 3600 Å (ε = 7900). The *methyl* ester, obtained in 65% yield by the Fischer–Speier method, separated from methanol as pale yellow needles, m. p. 206° (Found: C, 42·5; H, 2·8; N, 14·1. $C_7H_6O_5N_2$ requires C, 42·4; H, 3·1; N, 14·1%). The *ethyl* ester was prepared in 69% yield by the same method; it separated as pale yellow needles, m. p. 165—167°, from benzene (Found: C, 45·4; H, 3·8; N, 13·4. $C_8H_8O_5N_2$ requires C, 45·3; H, 3·8; N, 13·2%).

3 : 5-*Dinitro-2-pyridone* (IV).—(*a*) 6-Hydroxynicotinic acid (2 g.) in nitric acid (20 c.c.; *d* 1·52) was heated under reflux for 30 hours. The solution was evaporated and the residue crystallised from water, giving 3 : 5-*dinitro-2-pyridone* (1·0 g.) as stout yellow needles, m. p. 175° (Found: C, 32·8; H, 1·9; N, 22·9. $C_5H_3O_5N_3$ requires C, 32·4; H, 1·6; N, 22·7%). Light absorption in water: Maxima at 2140 (ε = 13,400) and 3260 Å (ε = 11,400).

(*b*) 6-Hydroxy-5-nitronicotinic acid (1·0 g.) in nitric acid (10 c.c.; *d* 1·52) was heated under reflux for 30 hours to give 3 : 5-dinitro-2-pyridone (0·5 g.) as stout yellow needles (from water), m. p. 175° alone or mixed with a specimen prepared by method (*a*).

(*c*) Dry sodium nitrite (0·7 g.) was slowly added to sulphuric acid (15 c.c.; *d* 1·84) with shaking and gentle heating to complete solution. The solution was cooled to 30° and treated with 2-amino-3 : 5-dinitropyridine (0·92 g.) added in portions with stirring. The mixture was then stirred for 2 hours, the temperature falling to 10°. It was diluted with water (20 c.c.), kept at 10° for 30 minutes, and then treated with a solution of sodium hydroxide (15 g.) in water (30 c.c.). After the mixture had been shaken for 30 minutes at 30°, the solid was collected and crystallised from water, giving 3 : 5-dinitro-2-pyridone (0·8 g.) as pale yellow needles, m. p. 174—175° alone or mixed with a specimen prepared by method (*a*) (Found: C, 32·7; H, 1·6; N, 23·0%).

(*d*) 3-Nitro-2-pyridone (1 g.) was heated under reflux with nitric acid (10 c.c.; *d* 1·52) for 2 hours. The solution was evaporated and the residue crystallised from water, giving 3 : 5-dinitro-2-pyridone (0·3 g.) as pale yellow needles, m. p. 175° alone or mixed with a specimen prepared by method (*a*) (Found: C, 32·5; H, 1·6%). Light absorption in water: Maxima at 2120 (ε = 13,400) and 3300 Å (ε = 11,400).

(*e*) Similar treatment of 5-nitro-2-pyridone gave 3 : 5-dinitro-2-pyridone in 38% yield as pale yellow needles (from water), m. p. 175° alone or mixed with a specimen prepared by method (*a*) (Found: C, 32·7; H, 1·7%). Light absorption in water: Maxima at 2120 (ε = 13,000) and 3300 Å (ε = 12,300).

1 : 6-*Dihydro-6-keto-1-methyl-5-nitronicotinic Acid* (IX).—1 : 6-Dihydro-6-keto-1-methylnicotinic acid (30·6 g.) was dissolved in nitric acid (306 c.c.; *d* 1·52), the temperature being kept below 55°. The solution was maintained at 50—55° for 5 hours and then concentrated to a small bulk at the same temperature; this was diluted with water (200 c.c.) and neutralised with solid sodium hydrogen carbonate. When the mixture had cooled, a solid (*A*) was filtered off, the filtrate was acidified with concentrated hydrochloric acid, and the solid collected. Crystallisation of this from water gave 1 : 6-*dihydro-6-keto-1-methyl-5-nitronicotinic acid* (15·8 g.) as stout yellow needles, m. p. 217—222° (Found: C, 42·6; H, 3·0; N, 14·2. $C_7H_6O_5N_2$ requires C, 42·4; H, 3·1; N, 14·1%). Light absorption in water: Maxima at 2180 (ε = 18,100) and 3640 Å (ε = 6600).

Methyl ester. A mixture of the acid (1·98 g.), phosphorus pentachloride (4·2 g.), and phosphoryl chloride (2·0 g.) was heated under reflux for 1 hour. Excess of reagents was removed under reduced pressure and the residue was crystallised from methanol, giving the *methyl* ester (1·5 g.) as yellow needles, m. p. 147—149° (Found: C, 45·2; H, 3·7; N, 13·3. $C_8H_8O_5N_2$ requires C, 45·3; H, 3·8; N, 13·2%).

Ethyl ester. The acid (1·98 g.) was heated under reflux with thionyl chloride (10 c.c.) for 3 hours. The solution was concentrated under reduced pressure and the residue treated with ethanol (25 c.c.). The solid was recrystallised from ethanol, giving the *ethyl* ester (1·5 g.) as pale yellow needles, m. p. 124° (Found: C, 47·8; H, 4·4. $C_9H_{10}O_5N_2$ requires C, 47·8; H, 4·5%).

1-*Methyl*-3 : 5-*dinitro-2-pyridone* (XI).—(*a*) 1 : 6-Dihydro-6-keto-1-methylnicotinic acid (3·06 g.) was heated under reflux for 5 hours with nitric acid (30·6 c.c.; *d* 1·52), and the solution evaporated to dryness. The residue crystallised from water, giving 1-methyl-3 : 5-dinitro-2-pyridone (2·0 g.) as yellow leaflets, m. p. 178° undepressed when mixed with a specimen, m. p. 178°, prepared according to Fischer and Chur (*loc. cit.*) from 1-methyl-2-pyridone (Found: C, 36·5; H, 2·4; N, 21·1. Calc. for $C_6H_5O_5N_3$: C, 36·2; H, 2·5; N, 21·1%). Light absorption in water: Maxima at 2080 (ε = 20,600), 2180 (ε = 19,100), and 3100 Å (ε = 12,700).

(*b*) The solid (*A*) obtained during the preparation of 1 : 6-dihydro-6-keto-1-methyl-5-nitronicotinic acid was crystallised from water, giving 1-methyl-3 : 5-dinitro-2-pyridone (0·2 g.) as pale yellow plates, m. p. 178° alone or when mixed with a specimen prepared as described under (*a*).

(*c*) 1 : 6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (0·25 g.) was heated under reflux with nitric acid (5 c.c.; *d* 1·52) for 4 hours to give 1-methyl-3 : 5-dinitro-2-pyridone (0·2 g.) as pale yellow leaflets (from water), m. p. 177° undepressed when mixed with a specimen prepared as described under (*a*).

(*d*) 1-Methyl-3-nitro-2-pyridone (0·7 g.) was heated under reflux for 2 hours with nitric acid (10 c.c.; *d* 1·52). The solution was evaporated to dryness and the residue crystallised from water, giving 1-methyl-3 : 5-dinitro-2-pyridone (0·3 g.) as yellow leaflets, m. p. 175—177° alone or when mixed with a specimen prepared by method (*a*) (Found : C, 36·5; H, 2·6; N, 21·5%). Light absorption in water : Maxima at 2080 (ε = 20,600), 2180 (ε = 19,000), and 3080 Å (ε = 12,200).

(*e*) Similar treatment of 1-methyl-5-nitro-2-pyridone (0·7 g.) gave 1-methyl-3 : 5-dinitro-2-pyridone (0·5 g.) as yellow leaflets (from water), m. p. 177° alone or when mixed with preparation (*a*).

(*f*) A solution of 3 : 5-dinitro-2-pyridone (0·92 g.) and potassium hydroxide (0·28 g.) in water (10 c.c.) was evaporated to dryness. The solid was powdered and heated at 120° for 3 hours in a sealed tube with methanol (5 c.c.) and methyl iodide (3 c.c.). The solvent was evaporated and the residue crystallised from water (charcoal), giving 1-methyl-3 : 5-dinitro-2-pyridone (0·5 g.) as yellow leaflets, m. p. 178° undepressed when mixed with specimen (*a*).

Methyl 6-Bromo-5-nitronicotinate (XV, R = Me).—6-Hydroxy-5-nitronicotinic acid (1·84 g.) was added to a mixture of phosphorus tribromide (10 c.c.) and bromine (6·4 g.) and heated at 100° for 20 hours. The excess of phosphorus tribromide was removed under reduced pressure and the residue decomposed with methanol (20 c.c.). The residue obtained on evaporation below 30° was crystallised from light petroleum (b. p. 60—80°), giving *methyl 6-bromo-5-nitronicotinate* (1·6 g.) as pale yellow needles, m. p. 98° (Found : N, 10·6. $C_7H_5O_4N_2Br$ requires N, 10·7%).

Ethyl 6-Bromo-5-nitronicotinate (XV, R = Et).—This was obtained in 40% yield by a similar method; the *ester* separated from light petroleum (b. p. 60—80°) as pale yellow stout needles, m. p. 85° (Found : C, 35·0; H, 2·8; N, 10·1. $C_8H_7O_4N_2Br$ requires C, 34·9; H, 2·6; N, 10·2%).

Methyl 6-Chloro-5-nitronicotinate (XIV, R = Me).—A mixture of 6-hydroxy-5-nitronicotinic acid (0·92 g.), phosphorus pentachloride (3 g.), and phosphoryl chloride (5 c.c.) was heated at 100° for 2 hours. Excess of phosphoryl chloride was removed under reduced pressure and the residue treated with methanol (10 c.c.). Water (40 c.c.) was added and the precipitated solid crystallised from light petroleum (b. p. 60—80°) from which *methyl 6-chloro-5-nitronicotinate* (0·92 g.) separated as pale yellow leaflets, m. p. 76° (Found : C, 38·9; H, 2·3; N, 12·8. $C_7H_5O_4N_2Cl$ requires C, 38·8; H, 2·3; N, 12·9%).

Ethyl 6-Chloro-5-nitronicotinate (XIV, R = Et).—This was obtained in 44% yield by a similar method; the *ester* separated from aqueous ethanol as prisms, m. p. 61° (Found : C, 41·6; H, 3·3; N, 12·5. $C_8H_7O_4N_2Cl$ requires C, 41·7; H, 3·1; N, 12·2%).

2-Chloro-3 : 5-dinitropyridine (XVI).—A mixture of 3 : 5-dinitro-2-pyridone (0·92 g.), phosphorus pentachloride (1·5 g.), and phosphoryl chloride (2 c.c.) was heated at 120° in a sealed tube for 2 hours. Excess of phosphoryl chloride was removed under reduced pressure, and the residue treated with water (15 c.c.) and basified with sodium hydroxide solution with cooling. The solid was separated and crystallised from light petroleum (b. p. 60—80°) from which *2-chloro-3 : 5-dinitropyridine* (0·5 g.) separated as laminæ, m. p. 64° (Found : N, 20·5. $C_5H_2O_4N_3Cl$ requires N, 20·6%).

5-Chloro-3-nitro-2-pyridone (XX).—A solution of 2-amino-5-chloro-3-nitropyridine (1·25 g.) in sulphuric acid (4 c.c.; *d* 1·84) was diluted with water (2·5 c.c.). Sodium nitrite (1·0 g.) was added portionwise below 10° with stirring. Stirring was continued for 1 hour below 10°, and the cooled reaction mixture was then diluted with water (25 c.c.) and kept overnight at 0°. The solid which separated was crystallised from ethanol, giving *5-chloro-3-nitro-2-pyridone* (1·18 g.) as yellow prisms, m. p. 235° (Found : C, 34·7; H, 1·5. $C_5H_3O_3N_2Cl$ requires C, 34·4; H, 1·7%).

5-Chloro-1-methyl-3-nitro-2-pyridone (XVIII).—A solution of 5-chloro-3-nitro-2-pyridone (1·75 g.) in aqueous potassium hydroxide (10 c.c.; 6%) was evaporated to dryness. The powdered potassium salt was heated under reflux for 2 hours in ethanol (10 c.c.) with methyl iodide (4·0 g.). The mixture was filtered from solid material which was washed with benzene. The filtrate and washings were evaporated under reduced pressure and the residue crystallised from benzene–light petroleum (b. p. 60—80°) (charcoal) from which *5-chloro-1-methyl-3-nitro-2-pyridone* (0·5 g.) separated as small, pale yellow prisms, m. p. 126° (Found : C, 38·8; H, 2·7; N, 14·7. $C_6H_5O_3N_2Cl$ requires C, 38·2; H, 2·7; N, 14·9%). A mixture with the compound (m. p. 115°) obtained by the chlorination of 1-methyl-3 : 5-dinitro-2-pyridone had m. p. 85—95°.

2-Amino-3-chloro-5-nitropyridine (XXI).—2-Amino-5-nitropyridine (1·39 g.) was dissolved in ethanol (100 c.c.) and treated with chlorine (0·71 g.) with ice-cooling. The solution was evaporated under reduced pressure, water (20 c.c.) added, and the insoluble material filtered off, washed with water, and dried. Crystallisation from ethanol (charcoal) gave 2-amino-3-chloro-5-nitropyridine (0·85 g.) as pale yellow needles, m. p. 211—213° (Bystritskaya and Kirssanow, *loc. cit.*, give m. p. 205—206°) (Found : N, 24·4. Calc. for $C_5H_4O_2N_3Cl$: N, 24·2%).

3-Chloro-5-nitro-2-pyridone (XXII).—The preparation of this compound by the action of hydrochloric acid at 150° on 2 : 3-dichloro-5-nitropyridine is described in U.S.P. 1,778,784, but we have not found any reference in the literature to the preparation of the latter compound (cf. D.R.-P. 597,974). 2-Amino-3-

chloro-5-nitropyridine (0·35 g.) in sulphuric acid (1·0 c.c.; *d* 1·84) and water (0·5 c.c.) was cooled below 10° and treated with sodium nitrite (0·3 g.) added in portions with shaking. After being shaken for a further hour, the mixture was diluted with water (6 c.c.), cooled to 0°, and filtered. Crystallisation of the residue from aqueous ethanol gave 3-chloro-5-nitro-2-pyridone (0·2 g.) as pale yellow prisms, m. p. 198° (U.S.P. 1,778,784 gives m. p. 198°) (Found: N, 16·5. Calc. for $C_5H_3O_3N_2Cl$: N, 16·0%).

3-Chloro-1-methyl-5-nitro-2-pyridone (XVII).—(*a*) A mixture of 1-methyl-3 : 5-dinitro-2-pyridone (1·99 g.), phosphorus pentachloride (3 g.), and phosphoryl chloride (2 c.c.) was heated in a sealed tube at 150° for 4 hours. The excess of phosphoryl chloride was removed under reduced pressure and the residue was treated with ice-water (15 c.c.) and made alkaline with potassium hydroxide solution. The mixture was extracted with cold benzene (20 c.c.), the insoluble 1-methyl-3 : 5-dinitro-2-pyridone (0·5 g.; m. p. 170—174°) separated, and the dried (Na_2SO_4) benzene extract evaporated. The residue was crystallised from ethyl acetate–light petroleum (b. p. 60—80°) (charcoal), giving *3-chloro-1-methyl-5-nitro-2-pyridone* (0·2 g.) as pale-yellow prisms, m. p. 115° (Found: C, 38·8; H, 2·5; N, 15·2. $C_6H_5O_3N_2Cl$ requires C, 38·2; H, 2·7; N, 14·9%).

(*b*) 1-Methyl-3 : 5-dinitro-2-pyridone (0·99 g.) and thionyl chloride (5 c.c.) were heated in a sealed tube at 140—150° for 5 hours. The excess of thionyl chloride was removed under reduced pressure and the residue shaken with hot benzene (10 c.c.). The mixture was cooled and filtered from unchanged 1-methyl-3 : 5-dinitro-2-pyridone (0·25 g.; m. p. 169—172°), the filtrate evaporated, and the residue crystallised from ethyl acetate–light petroleum (b. p. 60—80°) (charcoal), giving 3-chloro-1-methyl-5-nitro-2-pyridone (0·4 g.) as pale yellow prisms, m. p. 114—115° alone or mixed with a specimen prepared by method (*a*).

(*c*) A solution of 3-chloro-5-nitro-2-pyridone (1·75 g.) in aqueous potassium hydroxide (10 c.c.; 6%) was evaporated to dryness. The residue was heated under reflux with ethanol (10 c.c.) and methyl iodide (5 c.c.) for 2 hours, the solvent removed, and the residue extracted with hot benzene. The benzene extract was evaporated and the residue sublimed at 110°/10^{-3} mm. Crystallisation of the sublimate from ethyl acetate–light petroleum (b. p. 40—60°) gave 3-chloro-1-methyl-5-nitro-2-pyridone (1·5 g.) as prisms, m. p. 115° undepressed when mixed with the specimen prepared as described under (*a*) (Found: N, 15·0%).

Nitration of 2-pyridone, as described by Tschitschibabin and Schapiro (*loc. cit.*), gave a product which separated from ethanol as small yellow needles, m. p. 286° (decomp.) (Found: N, 16·5%). Light absorption in water: Maxima at 2160 Å ($E^{1\%}_{1\,cm.}$ = 580) and 3380 Å ($E^{1\%}_{1\,cm.}$ = 590). When heated on a spatula in a free flame it explodes violently; for this reason satisfactory carbon and hydrogen analyses could not be obtained.

Sodium 3-Nitro-2-pyridyl Oxide.—3-Nitro-2-pyridone (1·4 g.) was dissolved in hot sodium hydroxide solution (5%; 10 c.c.). The solid which separated on cooling was crystallised from aqueous ethanol, giving the *monohydrate* of sodium 3-nitro-2-pyridyl oxide (0·9 g.) as fine yellow needles, m. p. 340° (decomp.) (Found: N, 15·6. $C_5H_3O_3N_2Na,H_2O$ requires N, 15·6%). Light absorption in water: Maxima at 2580 (ε = 2400) and 3600 Å (ε = 6600).

Sodium 5-Nitro-2-pyridyl Oxide.—5-Nitro-2-pyridone was treated in a similar manner to give the trihydrate of sodium 5-nitro-2-pyridyl oxide as stout yellow needles (from aqueous ethanol), m. p. 318° (decomp.) (Found: N, 13·2. Calc. for $C_5H_3O_3N_2Na,3H_2O$: N, 13·0%) [Räth and Prange, *Ber.*, 1925, **58**, 1208, give m. p. 303° (decomp.) for the trihydrate obtained by the alkaline hydrolysis of 2-nitramino-5-nitropyridine]. Light absorption in water: Maxima at 2060 (ε = 9100) and 3020 Å (ε = 10,500).

Sodium 3 : 5-Dinitro-2-pyridyl Oxide.—Similar treatment of 3 : 5-dinitro-2-pyridone gave the *dihydrate* of sodium 3 : 5-dinitro-2-pyridyl oxide as long, pale yellow needles (from aqueous ethanol), m. p. 298° (decomp.) (Found: N, 17·0. $C_5H_2O_5N_3Na,2H_2O$ requires N, 17·3%). Light absorption in water: Maxima at 2100 (ε = 13,600) and 3260 Å (ε = 10,100).

The three sodium salts described above resemble Tschitschibabin and Schapiro's compound in that they decompose violently when heated.

3 : 5-Dinitro-2-pyridone (IV).—The compound, m. p. 286° (decomp.) (1·0 g.; see above), was heated under reflux with nitric acid (10 c.c.; *d* 1·52) for 2 hours. The residue obtained on evaporation was recrystallised from dilute hydrochloric acid, giving 3 : 5-dinitro-2-pyridone (0·7 g.) as pale yellow needles, m. p. 175° undepressed when mixed with an authentic specimen.

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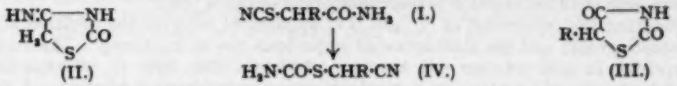
578. *The Structure of "isoThiohydantoin" and Related Compounds.*

By W. Davies and J. A. Maclaren.

Thiocyanatoacetamide (I; R = H) is claimed by Miolati (*Gazzetta*, 1893, **23**, I, 90) to isomerise to "*iso*thiohydantoin" (II), for which a new formula, cyanomethyl thiolcarbamate (IV; R = H) is now proposed. This is supported by the fission products of the compound and by its infrared spectrum. A rearrangement similar to that of (I; R = H) to (IV; R = H) is also found with α-thiocyanatopropionamide (I; R = Me) which is converted into 1-cyanoethyl thiolcarbamate (IV; R = Me). A probable mechanism of the rearrangement is suggested.

The chemistry of 2 : 4-diaminothiazoles (Davies, Maclaren, and Wilkinson, *J.*, 1950, 3491) drew attention to the only other 4-aminothiazole (or 4-iminothiazoline) previously described, the so-called "*iso*thiohydantoin" or 4-imino-2-ketothiazolidine (II). Thiocyanatoacetamide (I; R = H) was prepared by Miolati (*loc. cit.*) from chloroacetamide and potassium thiocyanate, and this compound was isomerised in dilute sulphuric acid to (II). This preparation was confirmed by Ganapathi and Venkataraman (*Proc. Indian Acad. Sci.*, 1945, **22**, 359), who also converted their product into 2 : 4-diketothiazolidine (III; R = H) by acid hydrolysis.



The structure of thiocyanatoacetamide itself has been queried by Frerichs and Beckurts (*Chem. Zent.*, 1900, **71**, I, 589), who suggested that it was an *iso*thiocyanato-compound. However, the work of Wheeler and Merriam (*J. Amer. Chem. Soc.*, 1901, **23**, 283) indicates that the above normal structure (I; R = H) is correct. On the other hand, the accepted structure (II) for "*iso*thiohydantoin" is surprising, since, by analogy with other 4-aminothiazoles (Davies, Maclaren, and Wilkinson, *loc. cit.*), (II) might be expected to darken rapidly in air, be easily acetylated, and be very unstable in acid solution. On the contrary, this compound is quite stable in air for many weeks, cannot be acetylated by the usual means, and is unaffected when dissolved at room temperature in 2N-sulphuric acid, in which it is obtained in 93% yield from (I).

It is found that "*iso*thiohydantoin" reacts with hot aniline to yield an unidentified thiol and *s*-diphenylurea, and that with a hot aqueous solution of mercuric chloride a crystalline mercury salt, $C_4H_4N_2S_2Hg$, is obtained. "*iso*Thiohydantoin" also reacts in alcoholic solution with an equimolar mixture of chloro-2 : 4-dinitrobenzene and sodium hydroxide to yield a yellow crystalline sulphide, $C_9H_5O_4N_3S$. These three reactions, which cannot be easily understood on the basis of structure (II), are readily explicable if we assume that "*iso*thiohydantoin" is cyanomethyl thiolcarbamate (IV; R = H). From the known general reactions of thiolcarbamates (Davies and Maclaren, *J.*, 1951, 1434), it is seen that the reaction with aniline has proceeded thus :

$$R{\cdot}CH(CN){\cdot}S{\cdot}CO{\cdot}NH_2 + 2NH_2Ph \longrightarrow CO(NHPh)_2 + R{\cdot}CH(CN){\cdot}SH + NH_3$$

Similarly, the product of the reaction with mercuric chloride is the mercuric salt of mercaptoacetonitrile (thioglycollonitrile) (V; R = H) :

$Hg(S{\cdot}CHR{\cdot}CN)_2$	$C_6H_3(NO_2)_2{\cdot}S{\cdot}CHR{\cdot}CN$	$C_2H_5{\cdot}O{\cdot}CS{\cdot}NH_2$	$R{\cdot}S{\cdot}CO{\cdot}NH_2$	$S(CH_2{\cdot}CN)_2$
(V.)	(VI.)	(VII.)	(VIII.)	(IX.)

Hydrolysis of the thiolcarbamate group to thiol has occurred also in the reaction with alkaline chloro-2 : 4-dinitrobenzene, since the product is undoubtedly 2 : 4-dinitrophenylthioacetonitrile (VI; R = H). This reaction with thiolcarbamates is found to be a general one; *e.g.*, methyl thiolcarbamate (VIII; R = Me) yields 2 : 4-dinitrophenyl methyl sulphide, fission again occurring between the sulphur atom and the carbamyl group.

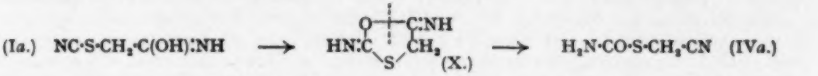
The accepted structure of "*iso*thiohydantoin" is chiefly based on its conversion by acid hydrolysis into 2 : 4-diketothiazolidine (III; R = H). However, this observation does not conflict with the structure now proposed (IV; R = H) since similar treatment of α-thiocyanatoamides and esters (Miolati, *loc. cit.*; also Wheeler and Barnes, *Amer. Chem. J.*, 1900, **24**, 80)

gives the corresponding 2 : 4-diketothiazolidine (III). Alternatively, the unknown thiazolidine (II) may well be a still-unisolated intermediate in the conversion of (IV; R = H) into (III; R = H). Finally an examination of the infra-red spectrum of "*iso*thiohydantoin" reveals bands which are quite compatible with the proposed structure (IV; R = H) but not with (II) or its amino- or enolic tautomers.

A rearrangement similar to that of (I; R = H) to (IV; R = H) is also found with α-thiocyanatopropionamide (I; R = Me) which forms 1-cyanoethyl thiolcarbamate (IV; R = Me). In exactly the same way as its lower homologue, this ester yields the mercuric salt of α-mercaptopropionitrile (V; R = Me), and α-(2 : 4-dinitrophenylthio)propionitrile (VI; R = Me); likewise, *s*-diphenylurea is formed when the compound is heated with aniline. On the other hand, all attempts to isomerize α-thiocyanatophenylacetamide (I; R = Ph) and α-selenocyanatoacetamide (I; R = H, Se for S) have been unsuccessful.

The most direct proof of the structures of "*iso*thiohydantoin" and its homologue would be to synthesise them by another means, and two methods have been tried unsuccessfully. Chloroacetonitrile does not react with ethyl thioncarbamate (VII) to form the desired product, but instead causes a rearrangement to form ethyl thiolcarbamate (VIII; R = Et), and this is true in all solvents tried (cf. Davies and Maclaren, *loc. cit.*). The same isomerization also occurs with α-chloropropionitrile. According to Fleischer's results (*Ber.*, 1876, **9**, 991), cyanomethyl thiolcarbamate would be expected from the interaction of chloroacetonitrile and ammonium thiolcarbamate (VIII; R = NH_4). However, it is now found that the only product isolated from this vigorous reaction is biscyanomethyl sulphide (IX).

It is seen that the conversion of (I) into (IV) apparently involves the addition of water to the thiocyanato-group, and the abstraction of water from the amido-group. The first reaction is not surprising in acid solution (cf. Arapides, *Annalen*, 1888, **249**, 7), whereas the almost complete dehydration of an amide to a nitrile is not usual in aqueous solution. A hydrolytic environment seems essential to the change, which has only been effected in acid and so far has not been wrought by heat alone. However, the driving force of the reaction cannot be the tendency to form a strong base in acid, since (IV; R = H) is readily extracted with ether from 2N-sulphuric acid. A likely intermediate in the rearrangement is the heterocyclic compound



(X) which would be formed by internal condensation of the hydroxy-form (I*a*) of (I; R = H), in the same way as γ-hydroxycrotononitrile gives unstable α-aminofuran (Culvenor, Davies, and Haley, *J.*, 1950, 3123). Fission of (X) as shown by the dotted line would yield (IV*a*). The implications of this type of change will be considered in a later communication.

Experimental.

Preparation of α-Thiocyanato-amides.—Thiocyanatoacetamide was prepared according to Miolati (*loc. cit.*).

α-Chloropropionamide (25 g.) and potassium thiocyanate (25 g.) were refluxed in 80% alcohol (100 ml.) for 4 hours. The precipitated ammonium chloride was filtered off, and the filtrate was evaporated on the water-bath to yield a yellow oil. This oil was continuously extracted with hot benzene, and the extract on cooling deposited the product as long colourless needles. *α-Thiocyanatopropionamide* (I; R = Me), recrystallized from benzene, had m. p. 86—86·5° (Found: N, 21·3; S, 24·4. $C_4H_6ON_2S$ requires N, 21·5; S, 24·6%).

α-Bromophenylacetamide (10 g.) and potassium thiocyanate (5 g.) were refluxed in 90% alcohol (150 ml.) for 1½ hours; the solvent was then evaporated, and the residue recrystallized from water as colourless needles of *α-thiocyanatophenylacetamide* (I; R = Ph), m. p. 143—145° (Found: C, 56·5; H, 4·3. $C_9H_8ON_2S$ requires C, 56·3; H, 4·2%).

Selenocyanatoacetamide was prepared by the method of Frerichs (*Abs.*, 1903, **84**, i, 609).

Cyanomethyl Thiolcarbamate ("iso*Thiohydantoin*").—Miolati's instructions (*loc. cit.*) are misleading, since if the acid concentration is greater than 10N., no yield is obtained. Finely powdered thiocyanatoacetamide (2 g.) was suspended in 2N-sulphuric acid (20 ml.), and the mixture kept at room temperature for 2 days. The resulting clear solution was extracted with ether (3 × 15 ml.), and the dried extract (Na_2SO_4) gave the thiolcarbamate (IV; R = H), which crystallized from chloroform as colourless needles (1·85 g., 93%), m. p. 74—75·5° (Found: C, 31·0; H, 3·4; N, 24·5. Calc. for $C_3H_4ON_2S$: C, 31·2; H, 3·4; N, 24·2%). This compound showed no basic properties, but was readily soluble in water. Precipitates were obtained on mixing its aqueous solution with aqueous solutions of silver nitrate, mercuric chloride, or copper sulphate. When heated with acetic anhydride and a few drops of pyridine, it produced a black tar.

Under exactly the same conditions as the above α-thiocyanatopropionamide was isomerized to form *1-cyanoethyl thiolcarbamate* (IV; R = Me), which crystallized from benzene–light petroleum as colourless micro-rhombs, m. p. 60—63°, in 90% yield (Found: C, 36·4; H, 4·5. $C_4H_6ON_2S$ requires C, 36·9; H, 4·6%).

Elementary selenium was the only product isolated when selenocyanatoacetamide was treated with 2N-sulphuric acid as above.

α-Thiocyanatophenylacetamide was treated with sulphuric acid of concentrations varying from 2N. to 20N., with sulphuric acid in alcohol, and with dry hydrogen chloride in alcohol, but in no case could any product be isolated corresponding to (IV).

Reactions of Cyanomethyl Thiolcarbamate and Related Compounds.—The thiolcarbamate (0·5 g.) in a mixture of alcohol (5 ml.) and concentrated hydrochloric acid (5 ml.) was refluxed for 2 hours, then concentrated to half its volume and diluted with water. The precipitate, which formed on cooling, crystallized from water as colourless needles, m. p. 125—126°, identical with 2 : 4-diketothiazolidine (III; R = H).

Under exactly the same conditions, α-thiocyanatophenylacetamide yields 2 : 4-diketo-5-phenylthiazolidine (III; R = Ph), m. p. 130—132°.

Reaction with aniline. When equal weights of the thiolcarbamate and aniline were heated together gently in a test-tube, a vigorous reaction occurred, ammonia and a thiol were evolved, and the mixture solidified. The product was filtered off from a small amount of oil, washed with 50% acetic acid, and crystallized from alcohol, forming needles, m. p. 237—238°, undepressed by admixture with *s*-diphenylurea. No other product could be isolated, and the reaction proceeded in exactly the same manner with the higher homologue.

Reaction with mercuric chloride. Hot aqueous solutions of cyanomethyl thiolcarbamate (0·5 g.) and mercuric chloride (1·0 g.) were mixed, and the mixture was boiled and allowed to cool. The precipitate was filtered off, washed with water, and crystallized from water or aqueous alcohol, forming colourless plates of the *mercury* derivative (V; R = H), m.p. 127—128° (Found: C, 14·0; H, 1·5; S, 18·6. $C_4H_4N_2S_2Hg$ requires C, 13·9; H, 1·2; S, 18·6%).

Similarly, 1-cyanoethyl thiolcarbamate is converted into the *mercury* derivative (V; R = Me), which crystallizes from alcohol as colourless needles, m. p. 139° (Found: C, 20·0; H, 2·5; N, 7·3. $C_6H_8N_2S_2Hg$ requires C, 19·2; H, 2·2; N, 7·5%).

Reaction with chloro-2 : 4-dinitrobenzene. To cyanomethyl thiolcarbamate (0·4 g.) and chloro-2 : 4-dinitrobenzene (0·4 g.) in alcohol (5 ml.), sodium hydroxide (0·16 g.) in 80% alcohol (5 ml.) was added. After 1 hour at room temperature, the resulting crystalline precipitate (0·2 g.), had m. p. 139—140°, and dilution of the filtrate with water yielded a further crop (0·25 g., m. p. 137—139°) of 2 : 4-*dinitrophenylthioacetonitrile* (VI; R = H). It crystallized from alcohol as pale yellow needles, m. p. 139·5—140·5° (Found: C, 40·1; H, 2·3; S, 13·3. $C_8H_5O_4N_3S$ requires C, 40·2; H, 2·1; S, 13·4%).

Similarly, the cyanoethyl ester gave α-(2 : 4-*dinitrophenylthio*)*propionitrile* (VI; R = Me) as pale yellow plates (alcohol), m. p. 108·5—109° (Found: C, 42·7; H, 2·9. $C_9H_7O_4N_3S$ requires C, 42·6; H, 2·8%.

Also methyl thiolcarbamate (VIII; R = Me) yielded methyl 2 : 4-dinitrophenyl sulphide, m. p. 127—128°. Bost, Turner, and Norton (*J. Amer. Chem. Soc.*, 1932, **54**, 1985) report m. p. 128°.

Attempted Syntheses of α-Cyanomethyl Thiolcarbamates (IV).—Chloroacetonitrile (3·2 ml.) and ethyl thioncarbamate (VII) (5·25 g.), dissolved in alcohol, were kept at 40° for 6 days. The precipitated ammonium chloride was filtered off, and the filtrate evaporated to yield a yellow liquid which solidified. The crystals were filtered off, washed with methanol, and recrystallized from benzene–light petroleum; they had m. p. 102·5—103·5°, undepressed by admixture with ethyl thiolcarbamate (VIII; R = Et).

α-Chloropropionitrile was synthesised by a new method based on Darzens's reaction (*Compt. rend.*, 1911, **152**, 1601). Acetaldehyde cyanohydrin (35 g.) and pyridine (40 g.) were mixed, evolving heat. The mixture was cooled in an ice-bath, and thionyl chloride (62 g.) was added dropwise during 20 minutes with shaking. After 2 hours at room temperature, the mixture was heated in an oil-bath at 110° until no more sulphur dioxide was evolved, and then poured into brine (250 ml.). The mixture separated into two layers and was extracted with ether (4 × 100 ml.), and the combined extracts were dried ($CaCl_2$) and distilled. After two distillations α-chloropropionitrile was obtained as a colourless liquid, b. p. 120—122° (22·5 g., 50%).

α-Chloropropionitrile and ethyl thioncarbamate (VII) did not react when refluxed in benzene for 8 hours. An equimolar mixture of the reactants was refluxed without solvent for 1½ hours and then distilled under reduced pressure. Apart from unchanged reactants, the only other fraction isolated had b. p. 115—120°/28 mm. This solidified and crystallized from benzene–light petroleum as plates, m. p. 104—105°, identified as ethyl thiolcarbamate (VIII; R = Et).

Chloroacetonitrile (1·5 ml.) and ammonium thiolcarbamate (2 g.) (VIII; R = NH_4) were mixed in alcohol (5 ml.). After some minutes, the suspension boiled spontaneously and, after 3 hours, the mixture was evaporated to dryness and extracted with ether. This extract yielded a colourless oil, which solidified on cooling and crystallized from benzene–light petroleum as colourless plates, m. p. 45—46°, apparently biscyanomethyl sulphide (IX) (Found: C, 43·5; H, 3·6; S, 28·3. Calc. for $C_4H_4N_2S$: C, 42·8; H, 3·6; S, 28·5%). Steinkopf, Herold, and Stöhr (*Ber.*, 1920, **53**, 1012) give 47·5°. The same product was obtained when the reactants were mixed alone; the reaction proceeds spontaneously and must be moderated by external cooling.

Infra-red Spectra.—We thank Dr. J. B. Willis, of C.S.I.R.O., for the following report: "Thiocyanatoacetamide (I; R = H), examined as a suspension in 'Nujol,' gave a band at 2166 cm.$^{-1}$,

due to the C≡N vibration. Bands were also found at 1600 cm.$^{-1}$ (NH bonding) and 1686 cm.$^{-1}$ (C=O stretching). '*iso*Thiohydantoin' gave a band at 2257 cm.$^{-1}$, which is attributed to a C≡N vibration, and bands at 1621 and 1698 cm.$^{-1}$. This is quite compatible with the formula proposed (IV; R = H) but not with the alternative formulæ (II, or its amino- or enol tautomers)."

Microanalyses were carried out under the direction of Dr. W. Zimmermann and Mr. N. L. Lottkowitz. The authors thank the Commonwealth National Health and Medical Research Council for a grant (to J. A. M.), and Dr. A. H. Cook, F.R.S., for advice.

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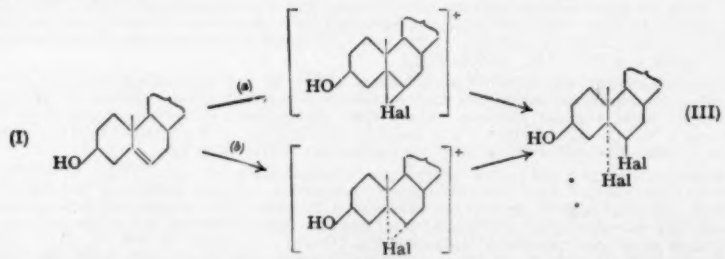
579. *The Stereochemistry of Steroids. Part V.* The Stereochemical Course of the Addition of Halogens to Cholesterol.*

By D. H. R. BARTON, E. MILLER, and H. T. YOUNG.

On treatment with thionyl chloride or phosphorus pentachloride 5α-chloro-6β-hydroxycholestan-3β-yl benzoate affords cholesteryl benzoate dichloride. Similarly the corresponding 5α-bromo-compound gives 5α-bromo-6β-chlorocholestan-3β-yl benzoate. The significance of these findings is discussed (*a*) in confirming the configurations previously assigned to the cholesterol dihalides and (*b*) in demonstrating the kinetically controlled non-Markownikoff opening of the α-halonium ions postulated as intermediates in the addition of halogens to cholesterol.

THE addition of molecular chlorine or bromine to cholesterol (I) affords the corresponding dichloride or dibromide (II; Hal = Cl or Br respectively). These compounds are well-characterised derivatives which have been known for many years. In Parts I and II of this series (Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, 1066) it was proved that the configuration at $C_{(6)}$ was β in both cases. Accepting the well-established rule of *trans*-addition of ionic-type reagents we concluded that, of the two formal possibilities (III) and (IV), (III) correctly represented the configurations at both $C_{(5)}$ and $C_{(6)}$. Various elimination reactions provided strong support for our views. However, in a paper which appeared simultaneously with ours, Rivett and Wallis (*J. Org. Chem.*, 1950, **15**, 35) recorded the opinion that these dihalides should be represented by (IV). Their argument for the assignment of the β-configuration at $C_{(5)}$ is mechanistically weak as we have already commented (Barton and Miller, *loc. cit.*). Nevertheless we felt it desirable to obtain additional and more direct evidence on the configurations at $C_{(5)}$ in order to place our conclusions beyond doubt. As will be clear from the sequel other interesting theoretical questions were also answered by our experiments.

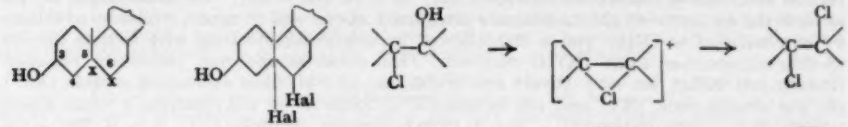
The elegant investigations by Winstein and his colleagues (series of papers in the *J. Amer. Chem. Soc.*, on "The Role of Neighbouring Groups in Replacement Reactions") on the stereochemical course of (*inter al.*) the replacement reactions of bromohydrins, and by Lucas and Gould (*ibid.*, 1941, **63**, 2541) on the corresponding reactions of chlorohydrins, can be applied to the present problems.



Lucas and Gould demonstrated that when a chlorohydrin (V) is treated with thionyl chloride or with phosphorus pentachloride the corresponding dichloride (VI) is formed, *via* the chloronium

* Part IV, *J.*, 1951, 1048.

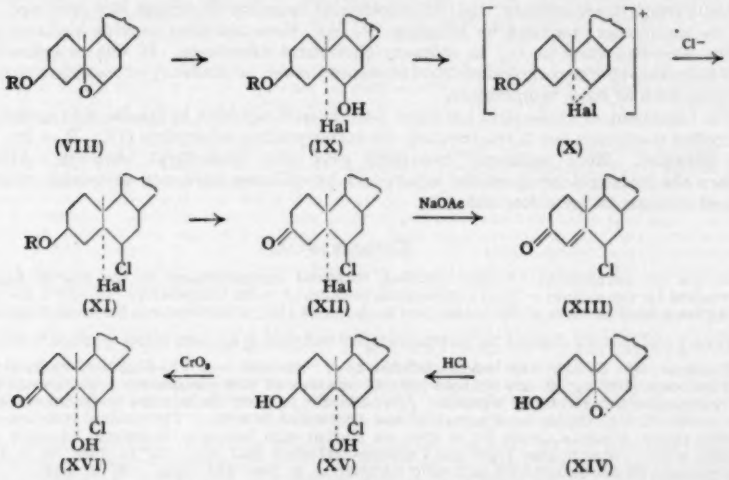
ion (VII), with complete retention * of configuration as a result of successive inversions: V → VII → VI. This important finding was applied in the cholesterol series in the following way. Cholesteryl benzoate β-oxide (VIII; R = Bz), when treated with hydrogen chloride (Spring and Swain, *J.*, 1939, 1356), gave 5α-chloro-6β-hydroxycholestan-3β-yl benzoate (IX;



(II; X = Hal) (IV) (V) (VII) (VI)

R = Bz, Hal = Cl). With both thionyl chloride and phosphorus pentachloride the latter furnished, *via* the chloronium ion (X; R = Bz, Hal = Cl), a dichloride (XI; R = Bz, Hal = Cl). This dichloride, obtained in both cases in good yield, was identified as cholesteryl benzoate dichloride. The α-configuration at $C_{(5)}$ in the latter is thus confirmed.

In principle there are two possible stereochemical routes for the formation of the cholesterol dihalides. These involve either (*a*) Markownikoff addition or (*b*) non-Markownikoff addition of Hal^- to the intermediate halonium ion. Previously (*loc. cit.*, p. 1066) we had assumed, principally from analogy with the addition reactions of iodine chloride (see Dewar, "The Electronic Theory of Organic Chemistry," Oxford Univ. Press, p. 143), that (*a*) would be the preferred path for the reaction. However in a recent review of the stereochemistry of steroids



(VIII) (IX) (X) (XI) (XII) (XIII) (XIV) (XV) (XVI)

Fieser (*Experientia*, 1950, **6**, 312) suggested that the cholesterol dihalides were formed by route (*b*). Clearly the reactions reported immediately above confirm Fieser's views in so far as the formation of cholesterol dichloride is concerned. It was of interest, therefore, to determine whether the kinetically controlled addition of bromine to cholesterol followed a route through the 5 : 6α-bromonium ion.

Treatment of cholesteryl benzoate β-oxide with aqueous hydrobromic acid gave 5α-bromo-6β-hydroxycholestan-3β-yl benzoate (IX; R = Bz, Hal = Br) which, on reaction with both thionyl chloride and phosphorus pentachloride, gave the same cholesteryl benzoate chlorobromide. The latter was shown to be 5α-bromo-6β-chlorocholestan-3β-yl benzoate (XI;

* Lucas and Gould, and also Winstein and his colleagues, worked with symmetrical olefins. Therefore, in the case of unsymmetrically substituted cyclic olefins such as cholesterol, it can only be concluded that, if one employs a *trans*-chloro- or -bromo-hydrin, the dihalide produced will likewise be *trans*. The formation of either the 5α : 6β- or of the 5β : 6α-dihalide from the 5α-halogen-6β-hydroxyhydrin would be in agreement with the previous findings.

R = Bz, Hal = Br) in the following way. Reaction of cholesterol β-oxide (VIII; R = H) with aqueous hydrobromic acid afforded 5α-bromo-6β-hydroxycholestan-3β-ol (IX; R = H, Hal = Br) which with thionyl chloride gave 5α-bromo-6β-chlorocholestan-3β-yl chlorosulphinate (XI; R = Cl·SO·, Hal = Br). The last was not isolated but was decomposed by water to furnish 5α-bromo-6β-chlorocholestan-3β-ol (XI; R = H, Hal = Br). On benzoylation of this alcohol the 5α-bromo-6β-chloro-benzoate mentioned above was obtained, whilst by oxidation by chromic acid to (XII; Hal = Br) followed by dehydrobromination with sodium acetate 6β-chlorocholest-4-en-3-one (XIII) resulted. This chloro-ketone was previously obtained (Barton and Miller, *loc. cit.*; Rivett and Wallis, *loc. cit.*) (*a*) from cholesterol α-oxide (XIV) *via* the chlorohydrin (XV) and the ketone (XVI) followed by dehydration, a route which establishes the configuration at $C_{(6)}$, and (*b*) from cholesterol dichloride (XI; R = H, Hal = Cl) through the ketone (XII; Hal = Cl).

These experiments confirm Fieser's views of the stereochemical course of the formation of cholesterol dibromide, showing that the bromonium ions (X; R = Bz, Hal = Br) and (X; R = H, Hal = Br) are, from the Markownikoff point of view, opened abnormally. It would appear that the opening of the 5 : 6α-bromonium ion parallels sterically the opening of the 5 : 6-α-oxide ring.

In Part II of this series (Barton and Miller, *loc. cit.*) it was shown that ordinary cholesteryl benzoate dibromide with the 5α : 6β-configuration rearranged when kept in chloroform solution, to give the thermodynamically more stable 5β : 6α-dibromide. This rearrangement may complicate study of the reactions of 5α-bromo-6β-hydroxy-compounds. Thus when 5α-bromo-6β-hydroxycholestan-3β-yl benzoate (IX; R = Bz, Hal = Br) was treated with phosphorus tribromide on the steam-bath, 5β : 6α-dibromocoprostan-3β-yl benzoate resulted. However at room temperature ordinary (5α : 6β-)cholesteryl benzoate dibromide was produced. Following the arguments presented by Winstein (*loc. cit.*) these reactions provide confirmatory proof of the α-configuration at $C_{(5)}$ in ordinary cholesterol dibromide. It was of interest to note that 5α-bromo-6β-chlorocholestan-3β-yl benzoate showed no tendency to undergo rearrangement in chloroform at room temperature.

On treatment of cholesterol benzoate β-oxide with aqueous hydriodic acid under carefully controlled conditions (see Experimental) the corresponding iodohydrin (IX; R = Bz, Hal = I) was obtained. More prolonged treatment gave only cholesteryl benzoate. Attempts to replace the hydroxyl group of the iodohydrin by chlorine were not successful owing to the ease of elimination (of iodine chloride).

Experimental.

M. p.s are uncorrected. Unless specified, rotations (approximated to the nearest degree) were determined for the sodium D line in chloroform solution at room temperature (15—25°), the specimens having been dried *in vacuo* at 20° below their m. p.s or at 110°, whichever was the lower temperature.

Savory and Moore's alumina for chromatography was used in all cases unless specified to the contrary.

Reactions of 5α-Chloro-6β-hydroxycholestan-3β-yl Benzoate.—(i) 5α-Chloro-6β-hydroxycholestan-3β-yl benzoate (100 mg.) in dry benzene (20 ml.) was treated with phosphorus pentachloride (100 mg.), and the mixture refluxed for 30 minutes. After addition of water the mixture was refluxed for a further 10 minutes and the benzene layer separated and evaporated *in vacuo*. The residual gum was chromatographed (Birlec alumina Grade H) to give, on elution with benzene, cholesteryl benzoate dichloride (70 mg.) which, recrystallised from ethyl acetate–methanol, had $[\alpha]_D$ −20° (*c*, 2·00), m. p. 129—130°, not depressed on admixture with authentic material, m. p. 130—131°, $[\alpha]_D$ −20° (*c*, 2·28).

(ii) 5α-Chloro-6β-hydroxycholestan-3β-yl benzoate (50 mg.) was treated with pure thionyl chloride (0·5 ml.) and kept at room temperature for 48 hours. The excess of thionyl chloride was removed *in vacuo* and the residue chromatographed over alumina. Elution with 40% benzene–light petroleum (b. p. 40—60°) afforded cholesteryl benzoate dichloride (60%) which, recrystallised from ethyl acetate–methanol, had $[\alpha]_D$ −25° (*c*, 2·48), m. p. 130—131°, undepressed on admixture with authentic material (see above).

(iii) 5α-Chloro-6β-hydroxycholestan-3β-yl benzoate (100 mg.) was treated with dry pyridine (2 ml.) and pure thionyl chloride (1 ml.) according to the experimental procedure of Lucas and Gould (*loc. cit.*). After working up, chromatography (eluant, 50% benzene–light petroleum (b.p. 40—60°) afforded cholesteryl benzoate dichloride (15%), which, recrystallised from ethyl acetate–methanol, had m. p. 125—127°, not depressed on admixture with authentic material.

5α-Bromo-6β-hydroxycholestan-3β-yl Benzoate.—Cholesteryl benzoate β-oxide (400 mg.) in chloroform (25 ml.) was shaken with 48% aqueous hydrobromic acid (10 ml.) for 10 minutes. After the chloroform layer had been washed with dilute sodium sulphite solution and then with water, evaporation *in vacuo* afforded *5α-bromo-6β-hydroxycholestan-3β-yl benzoate*; recrystallised from ethyl acetate–methanol, this had m. p. 173—174°, $[\alpha]_D$ −22° (*c*, 3·28) (Found: Br, 14·9. $C_{34}H_{51}O_3Br$ requires Br, 13·6%).

(*a*) Treatment of this bromohydrin (400 mg.) with pure thionyl chloride (5 ml.) overnight, followed by removal of the excess of thionyl chloride *in vacuo* and chromatography over alumina (eluant, 50% benzene–light petroleum (b.p. 40—60°) afforded *5α-bromo-6β-chlorocholestan-3β-yl benzoate* (90%) which, recrystallised from ethyl acetate–methanol, had m. p. 124—125° (decomp.), $[\alpha]_D$ −35° (*c*, 1·79) (Found: Cl + Br, 19·45. $C_{34}H_{50}O_2ClBr$ requires Cl + Br, 19·45%). The rotation was unchanged during 8 days at room temperature.

(*b*) Treatment of the bromohydrin (100 mg.) in dry benzene (10 ml.) with phosphorus pentachloride (100 mg.) and refluxing for 15 minutes afforded, after working up as in experiment (i) above, the foregoing chloro-bromide (60%), m. p. 124—125°, undepressed in m. p. on admixture.

(*c*) Treatment of the bromohydrin (100 mg.) with phosphorus tribromide (0·5 ml.) at room temperature overnight afforded, after purification by chromatography (eluant, 50% benzene–light petroleum (b.p. 40—60°), cholesteryl benzoate dibromide (15%), m. p. 132—134° (decomp.) (from ethyl acetate–methanol) not depressed on admixture with authentic material, m. p. 135° (decomp.). This procedure, but with heating on the steam for 2 hours instead of storage at room temperature, gave the stereoisomeric 5β : 6α-dibromocoprostan-3β-yl benzoate, m. p. 163—164° (decomp.), undepressed on admixture with authentic material of the same m. p.

5α-Bromo-6β-hydroxycholestan-3β-ol.—Cholesterol β-oxide (300 mg.) was shaken with chloroform–48% aqueous hydrobromic acid (20 ml. each). There was a copious precipitate of the bromohydrin in the chloroform layer. Working up as in the similar preparation given above furnished an almost quantitative yield of *5α-bromo-6β-hydroxycholestan-3β-ol* which, recrystallised from methanol–light petroleum (b. p. 40—60°), had m. p. about 128° (decomp.), $[\alpha]_D$ −38° (*c*, 0·98) (Found: Br, 16·4. $C_{27}H_{47}O_2Br$ requires Br, 16·55%).

Treatment of this bromohydrin (500 mg.) with pure thionyl chloride (5 ml.) at room temperature for 2 days, followed by removal of the excess of thionyl chloride *in vacuo*, gave a gummy residue (presumably of the chlorosulphinate). This was digested with aqueous methanol. The insoluble matter was recrystallised from methyl alcohol and the first two crops of resinous material rejected. Further concentration gave a third crop, m. p. 139—142° (decomp.). This was chromatographed over alumina. Elution with benzene gave a small amount of resinous material, but elution with 5% methanol–ether afforded crystalline *5α-bromo-6β-chlorocholestan-3β-ol* (120 mg.), m. p. 146—147° (decomp.) (bath preheated to 60°) (from methanol), $[\alpha]_D$ −47° (*c*, 1·91) (Found: Cl + Br, 23·2. $C_{27}H_{46}OClBr$ requires Cl + Br, 23·0%). When this chlorobromide (30 mg.) reacted with benzoyl chloride (0·5 ml.) in dry pyridine (5 ml.) at room temperature for 1 hour it gave 5α-bromo-6β-chlorocholestan-3β-yl benzoate which, recrystallised from ethyl acetate–methanol, had m. p. 125—126° undepressed on admixture with the benzoate of m. p. 124—125°, prepared as described above.

5α-Bromo-6β-chlorocholestan-3β-ol (200 mg.) in "AnalaR" acetic acid (25 ml.) was oxidised by chromium trioxide (60 mg.) in water (2 drops) at 40°, the solution being heated for 1 hour. Extraction with ether and working up in the usual way afforded a crystalline residue, presumably 5α-bromo-6β-chlorocholestan-3-one. The latter was refluxed with anhydrous sodium acetate (220 mg.) in ethanol (10 ml.) for 30 minutes. Addition of water gave crude 6β-chlorocholest-4-en-3-one (120 mg.). After filtration through alumina this was recrystallised slowly from ethyl acetate to give 6β-chlorocholest-4-en-3-one, m. p. 129° (Found: Cl, 8·55. Calc. for $C_{27}H_{43}OCl$: Cl, 8·45%), undepressed on admixture with authentic material, m. p. 129—130° (Barton and Miller, *loc. cit.*) but depressed by 30° on admixture with authentic 6α-chlorocholest-4-en-3-one.

6β-Hydroxy-5α-iodocholestan-3β-yl Benzoate.—Cholesterol β-oxide (500 mg.) in chloroform (50 ml.) was cooled to −20° and mixed slowly with 55% aqueous hydriodic acid (25 ml.), the temperature being kept at −20°. The two-phase system was stirred at this temperature for 2 hours and then poured into excess of aqueous sodium hydrogen carbonate. After being washed with sodium sulphite solution and then with water the chloroform layer was evaporated *in vacuo*, to furnish in almost quantitative yield *6β-hydroxy-5α-iodocholestan-3β-yl benzoate*; recrystallised cautiously from ethyl acetate–methanol, this had m. p. about 105° (vigorous decomp.) (Found: I, 19·85. $C_{34}H_{51}O_3I$ requires, I, 20·0%).

Shaking 100-mg. portions of cholesteryl benzoate β-oxide in chloroform (20 ml.) with concentrated aqueous hydriodic acid at room temperature for 5—15 minutes and working up as above gave cholesteryl benzoate, m. p. 148—149°, undepressed on admixture with an authentic specimen. The identity was confirmed by hydrolysis to cholesterol.

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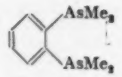
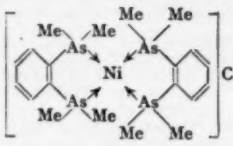
580. *Studies in Co-ordination Chemistry. Part IX.* Quadrivalent Nickel.*

By R. S. Nyholm.

The action of several oxidising agents on the compound $[NiCl_2(diarsine)_2]Cl$ has been studied, where "diarsine" represents *o*-phenylenebisdimethylarsine. Chlorine and ceric sulphate give rise to deep green compounds which are easily reduced. Concentrated nitric acid forms an intensely blue solution from which aqueous perchloric acid precipitates the deep blue compound $[NiCl_2(diarsine)_2][ClO_4]_2$. The chemical and physical properties of this compound indicate that the nickel atom is quadrivalent. The compound is diamagnetic as required for an octahedral complex of Ni(IV) with covalent $3d^24s4p^3$ bonds. The compound is practically insoluble in water but an aqueous suspension is easily reduced by sulphur dioxide to the yellow compound $[NiCl_2(diarsine)_2]ClO_4$. The corresponding bromide, $[NiBr_2(diarsine)_2][ClO_4]_2$, has been prepared also by the action of nitric acid and perchloric acid upon the compound $[NiBr_2(diarsine)_2]Br$. This new compound is deep green and is also diamagnetic. The properties of these compounds are discussed and the literature dealing with ter- and quadri-valent nickel is reviewed.

In Part V of this series (*J.*, 1950, 2061) the compounds formed by nickel salts with the ditertiary arsine chelate group *o*-phenylenebisdimethylarsine (I) were described. Bivalent nickel gives rise to a series of red complex salts with the general formula $[Ni(diarsine)_2]X_2$ (X = Cl, Br, I, CNS, ClO_4), as in (II); from the diamagnetism of these it is concluded that the four bonds to the metal atom are square planar, the bonds being $3d4s4p^2$. Oxidation of (II) with chlorine

(I.) 



(II.)

in aqueous solution, or preferably, with air and hydrochloric acid in alcoholic solution, gave a brownish-yellow compound with the formula $[NiCl_2(diarsine)_2]Cl$. The anion of this complex salt may be replaced by ClO_4^- and $\frac{1}{2}PtCl_6^{--}$; treatment of the compound with sodium bromide and thiocyanate in aqueous solution gives the corresponding bromide and thiocyanate, *i.e.*, $[NiBr_2(diarsine)_2]Br$ and $[Ni(CNS)_2(diarsine)_2]CNS$. The magnetic moments of these compounds (*ca.* 1·9 Bohr magnetons), as well as other chemical and physical properties, led to the conclusion that they are octahedrally co-ordinated complexes of tervalent nickel, as shown in (III), the two Cl atoms being shown as *trans* for convenience. The location of the unpaired electron is uncertain, but the use by the nickel atom of $3d^24s4p^3$ octahedral covalent bonds in the usual configuration scheme necessitates its promotion above the 4*p* level, probably into a 5*s* orbital (see Table I). Such a promotion should facilitate its removal by oxidation to give an octahedral diamagnetic complex of quadrivalent nickel, the latter then being isoelectronic with tervalent cobalt. Some evidence which suggested that this promotion took place was mentioned in Part V (*loc. cit.*); in a potentiometric titration, with ceric sulphate as the oxidant, it was shown that the bivalent compound $[Ni(diarsine)_2]Cl_2$ could be oxidised to the compound $[NiCl_2(diarsine)_2]Cl$ with an end-point after one equivalent of oxidising agent had been added. After the end-point had been passed further addition of ceric sulphate gave a deep green precipitate, and it was suggested that this might contain quadrivalent nickel.

The compound $[NiCl_2(diarsine)_2]Cl$ has now been treated with several other oxidising agents in an attempt to achieve this oxidation. When chlorine is bubbled through an aqueous solution of this substance the colour changes very quickly from a pale green to a deeper emerald-green. Addition of hydrochloric acid then yields a bright green precipitate; this substance is fairly soluble in water, and since it is precipitated by hydrochloric acid the anion

* Part VIII, *J.*, 1951, 1767.

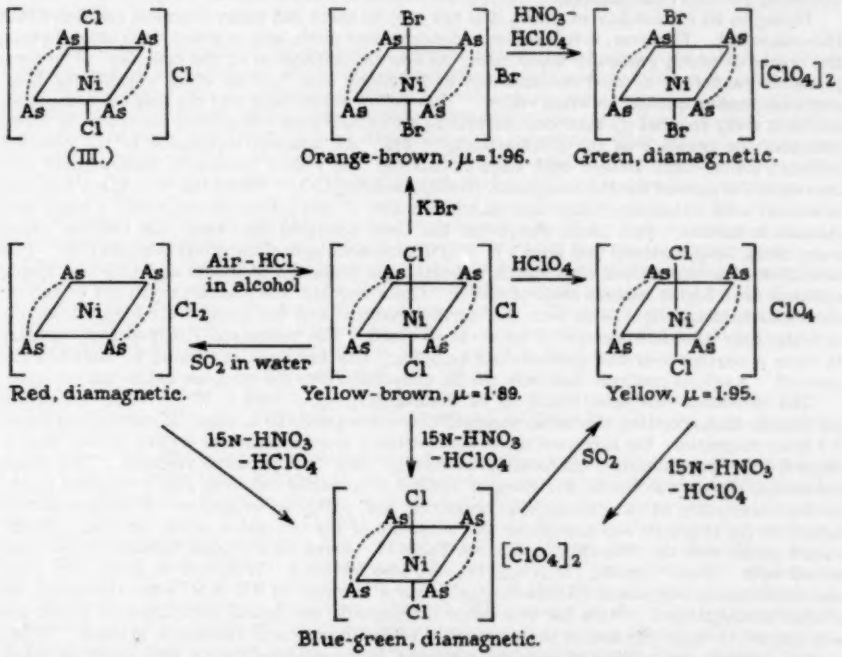
TABLE I.

Predicted magnetic moments for various nickel complexes.

Valency.	Bond type.	Unpaired electrons.	Calc. mag. moment (μ, B.M.).
II	Ionic (or $4s4p^3$ tetrahedral; or $4s4p^34d^2$ octahedral)	2	2·83
II	Covalent $3d4s4p^3$ square planar	0	0·00
II	Covalent $3d^24s4p^3$ octahedral	0 *	0·00
III	Ionic (or $4s4p^34d^2$ octahedral)	3	3·88
III	Covalent $3d^24s4p^3$ octahedral	1	1·73
IV	Ionic (or $4s4p^34d^2$ octahedral)	4	4·90
IV	Covalent $3d^24s4p^3$ octahedral	0	0·00

* It is assumed that 2 electrons are promoted to a 5*s* orbital in which they are paired.

is apparently the chloride ion. On storage, the compound becomes yellow within a few hours. Analysed after being dried in a desiccator in presence of chlorine, the compound contained about 90% of the chlorine required for the formula $[NiCl_2(diarsine)_2]Cl_2$. The magnetic susceptibility was not measured exactly, but the substance was paramagnetic and the paramagnetic susceptibility gradually increased. As this compound was clearly too unstable for investigation, the precipitation of the corresponding perchlorate was attempted. When



aqueous perchloric acid is added to the emerald-green solution obtained by chlorine oxidation, a green precipitate is obtained which is much less soluble than the chloride. The magnetic susceptibility of this compound ($\chi_g = 1{\cdot}0 \times 10^{-6}$) was less than that of the tervalent perchlorate $[NiCl_2(diarsine)_2]ClO_4$ for which $\chi_g = 1{\cdot}46 \times 10^{-6}$, suggesting that some formation of a diamagnetic complex had taken place; however, the chlorine analysis was too high for the compound $[NiCl_2(diarsine)_2][ClO_4]_2$ which one might expect to be formed. The method of oxidation appeared to be unsatisfactory probably because the dilution necessary to get the tervalent complex into aqueous solution resulted in some oxidation of the tertiary arsine. Both of these green compounds were easily reduced by sulphur dioxide. The chloride first becomes yellow and finally red, owing to the eventual formation of the $[Ni(diarsine)_2]^{++}$ ion. The perchlorate

was readily reduced to the yellow compound $[NiCl_2(diarsine)_2]ClO_4$, the insolubility of which makes it more resistant to the action of sulphur dioxide.

Treatment of an aqueous solution of $[NiCl_2(diarsine)_2]Cl$ with ceric sulphate in sulphuric acid solution gives a deep green precipitate, analysis of which suggests the formula $[NiCl_2(diarsine)_2][Ce(SO_4)_2]$, both metals being quadrivalent. The compound became yellow when kept. It was isolated in small amounts only, and the magnetic susceptibility was not measured. The freshly prepared compound reacts with aqueous perchloric acid to give a more stable deep blue-green compound, more easily prepared as follows.

Concentrated nitric acid has been found to be a very effective oxidising agent. When added to 15N-nitric acid, the finely divided tervalent compound $[NiCl_2(diarsine)_2]Cl$ dissolved at once to an intensely blue-black solution. The solution was treated almost immediately with perchloric acid, followed by a large volume of water, and a deep bluish-green precipitate was obtained. This substance is practically insoluble in water and its analysis agreed fairly closely with the formula $[NiCl_2(diarsine)_2][ClO_4]_2$; it does not contain nitrogen, confirming that the colour is not due to a nitrosyl group. Similar reactions occur when the compounds $[Ni(diarsine)_2]Cl_2$ and $[NiCl_2(diarsine)_2]ClO_4$ are treated with concentrated nitric acid and perchloric acid. The deep blue product is fairly stable on storage but undergoes some decomposition if left exposed to sunlight or when freely exposed to the atmosphere for some days, becoming yellow in the process.

Owing to its insolubility in water, it is not easy to carry out many chemical reactions with the compound. However, it redissolves in concentrated nitric acid to give a deep blue solution, the colour of which gradually fades owing to slow decomposition of the complex. The compound is unaffected by cold concentrated hydrochloric acid, but on being warmed the blue-green suspension quickly becomes yellow. This yellow suspension, and the original compound, are both easily reduced by stannous chloride to give a buff-pink precipitate, the colour of which indicates the presence of the $[Ni(diarsine)_2]^{++}$ ion. An aqueous suspension of the complex becomes yellow when treated with sulphur dioxide; the yellow product is paramagnetic and its analysis is correct for the compound $[NiCl_2(diarsine)_2]ClO_4$. When the blue-green complex is treated with potassium iodide and starch solution, a blue colour develops and a black precipitate is formed. This black compound has been described previously, its formula (when pure) being $NiI_2(diarsine)_2$ (see Part V); it is diamagnetic and of uncertain constitution. This formation of a blue colour with starch indicates the liberation of iodine and provides strong evidence for a higher valency state of nickel. Unfortunately, the reaction could not be carried out stoicheiometrically; since both the starting material and the product are highly insoluble in water only a limited amount of iodine is obtained. The compound $NiI_2(diarsine)_2$ appears to form a coating over the quadrivalent complex; this has been confirmed by isolating the product. Analysis confirms that only partial conversion into the complex iodide has occurred.

The substance has been found to be diamagnetic ($\chi_g = -0{\cdot}3 \times 10^{-6}$). After correction for atomic diamagnetism, the molar susceptibility corresponds to a magnetic moment of about 0·7 Bohr magneton; the corrected molar susceptibility is only about one-eighth of that usually observed for paramagnetic compounds containing only one unpaired electron. This small moment is clearly not due to any integral number of unpaired electrons and is ascribed partly to the uncertainty of the diamagnetic correction and partly to impurities. For comparative figures of the magnetic susceptibilities and moments of the complexes of bi-, ter-, and quadrivalent nickel with the ditertiary arsine, see Table II. Data for a typical bivalent nickel compound with " ionic " bonds, $[Ni(NH_3)_6]Br_2$, are also included. It should be noted that even the diamagnetic compound $[Ni(diarsine)_2]Cl_2$ has a moment of 0·5 B.M. after correction for atomic diamagnetism. Data for two other diamagnetic octahedral complexes of cobalt are also quoted to show the size of the moment after the diamagnetic correction is made. When used to indicate the number of unpaired electrons, it is considered that μ may safely be taken as formally zero when the corrected molar susceptibility from which it is calculated is less than 250, which is the case here.

As shown in Table I, diamagnetism is also expected for square four-covalent complexes of Ni(II) and for octahedral covalent $3d^24s4p^3$ Ni(II) complexes such as $[Ni(diarsine)_3][ClO_4]_2$. However, it has not been found possible to formulate the compound $[NiCl_2(diarsine)_2][ClO_4]_2$ as either of these stereochemical types whereas it is readily formulated as an octahedral Ni(IV) complex.

By treating the orange compound $[NiBr_2(diarsine)_2]Br$ with concentrated nitric acid followed by perchloric acid a similar reaction to that shown by the chloride takes place. A deep green perchlorate is obtained, analysis of which indicates the formula $[NiBr_2(diarsine)_2][ClO_4]_2$. Like

the corresponding chloride, this compound is diamagnetic. It reacts with potassium iodide–starch solution to give a blue colour and is reduced by sulphur dioxide to the orange perchlorate of the lower valency state.

TABLE II.

Magnetic susceptibilities (at 20°) of nickel complexes.

Valency of Ni.	Compound.*	χ_g.†	χ_M.†	Diamag. corrn.*	$\chi_{corr.}$.†	Moment (μ, B.M.).
II	$[NiX_2]Cl_2$	−0·50	−351	436	85	(0·5)
II	$[Ni(NH_3)_4]Br_2$	12·7	4099	152	4251	3·16
III	$[NiCl_2X_2]Cl$	1·41	1065	452	1517	1·89
III	$[NiCl_2X_2]ClO_4$	1·46	1170	455	1625	1·95
III	$[NiBr_2X_2]Br$	1·32	1150	489	1639	1·96
IV	$[NiCl_2X_2][ClO_4]_2$	−0·30	−272	478	206	(0·7)
IV	$[NiBr_2X_2][ClO_4]_2$	−0·29	−287	505	217	(0·7)
III	$[CoCl_2X_2]ClO_4$ [b]	−0·50	−365	455	90	(0·5)
III	$[Co\,en_3][ClO_4]_3$ [c]	−0·45	−155	210	55	(0·36)

* X = *o*-Phenylenebisdimethylarsine.

† χ_g = g.-susceptibility, χ_M = molar susceptibility, $\chi_{corr.}$ = latter after correction, × 10^{-6} in each case.

* The diamagnetism of the metal atom has been ignored in all cases. [b] Part VI, *J.*, 1950, 2071. [c] Asmussen, "Magnetokemiske Undersøgelser over Uorganiske Kompleksforbindelser," Copenhagen, 1944, p. 163.

On the basis, therefore, of the method of preparation of these compounds, which involves oxidation, and of the analyses, the action on reducing agents and on potassium iodide, and finally the diamagnetism, it seems reasonable to formulate both these compounds as octahedral complexes of quadrivalent nickel with covalent $3d^24s4p^3$ bonds. An *X*-ray crystallographic examination of these compounds is most desirable but in its absence their properties are most satisfactorily accounted for on the assumption that the nickel atom is quadrivalent. The compounds are therefore named: dichloro- and dibromo-di-*o*-phenylenebisdimethylarsine-nickel(IV) perchlorate. The relation between these compounds and other nickel complexes of the ditertiary arsine, showing the structures which are proposed for the new compounds, are summarised in the diagram, the two halogen atoms being shown as *trans* for convenience.

Unfortunately, it has not been found practicable to determine by direct measurement the oxidation–reduction potential of the tervalent–quadrivalent couple, as suggested by Mr. Terrey, but this can be estimated from the method of preparation. The oxidation is readily effected by ceric sulphate (*ca.* 1·6 v.), by chlorine (*ca.* 1·36 v.), and by concentrated nitric acid (which liberates chlorine from hydrogen chloride), so the E_0 value of the couple

$$[NiCl_2(diarsine)_2]^{++}/[NiCl_2(diarsine)_2]^{+}$$

would be approximately 1·3—1·4 v. The oxidation–reduction potential for the bivalent–tervalent couple with the diarsine, $[NiCl_2(diarsine)_2]^{+}/[Ni(diarsine)_2]^{++}$, is approximately 0·7 v. (see Part V, *loc. cit.*).

In view of the suggestion that the nickel atom is quadrivalent in the above compounds, it is of interest to review other evidence in the literature for ter- and quadri-valency of nickel in complex compounds. Much work has been done during the last few years but, earlier, Hofmann and Ehrhardt (*Ber.*, 1913, **46**, 1457) claimed to have prepared the compound trisodium hexaformoximonickelate(III), and Dubsky and Kuras (*Chem. Zentr.*, 1931, **102**, I, 2045) stated that they had isolated a tervalent nickel complex of benzamidoxime. Malatesta (*Gazzetta*, 1940, **70**, 842) disagreed with the conclusions of Dubsky and Kuras, showing that the compound is diamagnetic. Feigl (*Ber.*, 1924, **57**, 758) stated that the red solution obtained by treating nickel(II) bisdimethylglyoxime with ammonia in the presence of oxidising agents contained ter- or quadri-valent nickel. However, Okac and Polster (*Coll. Czech. Chem. Comm.*, 1948, **13**, 561, 572) have asserted that the oxime rather than the nickel undergoes oxidation; they claim that the red precipitate formed by neutralisation of the red oxidised solution is obtained only when lead dioxide is used as the oxidising agent, and that lead is an essential constituent of the red precipitate. The oxidation of square nickel complexes of dioximes has also been studied by Edelman (*J. Amer. Chem. Soc.*, 1950, **72**, 5765). By the action of bromine on nickel(II) bis-α-benzildioxime a dark brown compound, considered to be bis-α-benzildioxime-nickel(III) bromide, was isolated. This substance loses the bromine on moderate heating, reverting to the bivalent complex. The corresponding iodide was obtained as bronze crystals by a similar method of oxidation. Unfortunately, the magnetic moments were not reported. In oxidation of metal complexes in which the metal atom is attached to organic groups there

is always the possibility of oxidising the latter rather than the metal and the magnetic moment is therefore specially helpful. The possibility that the tertiary arsine rather than the nickel atom was being oxidised has been considered very carefully in all work with these ditertiary arsine complexes, but no evidence that this is taking place has been obtained. Edelman's compounds certainly appear to be tervalent, but in view of the previous uncertainty concerning the valency of the nickel atom in these compounds a more complete investigation of the physical properties and chemical reactions of the compounds formed by the oxidation of nickel complexes of dioximes would be desirable.

Jensen has also examined the action of halogens on square diamagnetic nickel(II) complexes. By the action of bromine on the red *trans*-bistriethylphosphinedibromonickel(II) the compound bistriethylphosphinetribromonickel(III), $NiBr_3,2PEt_3$, was obtained as violet-black crystals (*Z. anorg. Chem.*, 1936, **229**, 265). Later (*Acta Chem. Scand.*, 1949, **3**, 474) Jensen measured both the magnetic moment (1·7—1·9 B.M.) and the dipole moment (2·5 D.) and presented a sound case for the tervalency of the nickel atom, the co-ordination number of the metal atom being 5. The electric dipole moment was interpreted to mean that the shape of the molecule was a square pyramid. This substance might well be regarded as the first clearly established case for tervalent nickel in complex compounds. Jensen (*ibid.*, p. 481) also examined the action of atmospheric oxygen on the complexes of nickel with mono-, di-, and tri-aminoguanidine and suggested that the oxidation is initiated by the formation of a complex of ter- or quadri-valent nickel which then decomposes. The spontaneous oxidation of these compounds is remarkably fast.

The preparation of some complex heteropolymolybdates of quadrivalent nickel has been claimed by Hall (*J. Amer. Chem. Soc.*, 1907, **29**, 692); a compound of the formula $3BaO,NiO_2,9MoO_3,12H_2O$ was isolated. This substance is diamagnetic (Ray and Sarma, *Nature*, 1946, **157**, 627; *J. Ind. Chem. Soc.*, 1948, **25**, 205) from which it was concluded that octahedral covalent $3d^24s4p^3$ bonds are formed by a quadrivalent nickel atom. Ray and Sarma (*loc. cit.*) also described a dark purple periodate of the formula $Na(K)NiIO_6,xH_2O$ which is weakly paramagnetic (μ = 1·1—1·3 B.M.). The small paramagnetism was attributed to a slight amount of dissociation, it being claimed that the compound was an octahedral complex of quadrivalent nickel. Some difficulty was experienced in formulating this compound with the necessary six octahedral bonds. In view of the very electronegative groups to which the nickel(IV) is attached, the low moment is a little surprising at first sight, for it might be thought that the bonds would be ionic (μ = 4·90 B.M.). However, the isoelectronic cobalt(III) is diamagnetic even when connected to six oxygen atoms also, *e.g.*, in hydrated cobaltic sulphate. Lander (*Acta Cryst.*, 1951, **4**, 148; see also Lander and Wooten, *J. Amer. Chem. Soc.*, 1951, **73**, 2452) has recently described another quadrivalent nickel complex in which the nickel atom is connected to very electronegative groups. This is the compound $BaNiO_3$, obtained as a black powder. The magnetic moment (0·8 B.M.) is attributed to a small amount of dissociation. The crystal structure of this compound has been determined and it is found that the nickel atom is octahedrally co-ordinated to six oxygen atoms. A complex fluoride of quadrivalent nickel, K_2NiF_6, has been described by Klemm and Huss (*Z. anorg. Chem.*, 1949, **258**, 221), but its magnetic moment has not been reported.

The preparation of two binuclear quadrivalent nickel complexes in which the metal atom is octahedral has been reported by Hieber and Brücks (*Naturwiss.*, 1949, **36**, 312). On use, as the chelate group of *o*-mercaptoaniline, a deep blue complex was isolated, the structure of which is considered to involve a bridge of two oxygen atoms between two Ni(IV) atoms.

As the above summary indicates, the higher valency states of nickel offer a fruitful field for investigation; a more detailed study of the oxidation of square nickel complexes should prove very profitable.

Experimental.

Dichlorodi-o-phenylenebisdimethylarsinenickel (IV) *Perchlorate.*—The tervalent complex, $[NiCl_3(diarsine)_2]Cl$ (0·7 g.), prepared as in Part V, was very finely ground and added with stirring to cold 15N-nitric acid (30 ml.), giving a deep inky-blue solution, which was well stirred for 4 minutes, during which no change in colour was observed. After being filtered through a sintered-glass crucible, to remove any traces of insoluble matter, the blue solution was treated with 30% perchloric acid (10 ml.), followed immediately by distilled water (200 ml.), with vigorous stirring. A blue-black precipitate appeared and the solution was allowed to settle for 5 minutes. The *perchlorate* (0·78 g.) was then filtered off, well washed with distilled water, and dried *in vacuo* [Found: C, 27·0; H, 3·5; Cl (excluding ClO_4), 7·9; Ni, 6·8. $C_{28}H_{32}O_8Cl_4As_4Ni$ requires C, 26·65; H, 3·5; Cl (excluding ClO_4), 7·9; Ni, 6·52%]. No nitrogen was obtained in three separate determinations. The compound is insoluble in water and in organic solvents

but dissolves in concentrated nitric acid with eventual decomposition. When heated, it becomes red at about 190° and decomposes explosively at 270°.

Reduction with sulphur dioxide. The finely divided blue nickel(IV) compound, prepared as above (0·3 g.), was suspended in water (20 ml.), and sulphur dioxide passed into the suspension. The colour changed to yellow immediately. After a few minutes the yellow compound (0·25 g.) was filtered off, well washed with distilled water, and dried. It was then paramagnetic, reduction to the tervalent *perchlorate* $[NiCl_2(diarsine)_2]ClO_4$ having taken place [Found: C, 30·2; H, 4·15; Cl (excluding ClO_4), 8·65. $C_{20}H_{22}O_4Cl_3As_4Ni$ requires C, 29·95; H, 4·0; Cl (excluding ClO_4), 8·85%].

Action of Other Oxidising Agents on $[NiCl_2(diarsine)_2]Cl$.—*Chlorine.* The chloride (0·84 g.) was dissolved in distilled water (700 ml.), the solution filtered and cooled to 10°, and chlorine passed in for 3 minutes. The colour changed from a pale to a deep emerald-green. Excess of 30% perchloric acid (20 ml.) was then added, a green precipitate being formed, which during about 10 minutes gradually darkened in colour. The compound was then filtered off, washed with distilled water saturated with chlorine, and dried over concentrated sulphuric acid in a desiccator filled with chlorine. The compound (0·75 g.) was analysed and its magnetic moment determined as soon as it was dry {Found: C, 29·4; H, 3·9; Cl (excluding ClO_4), 10·0; Ni, 7·2%. Cf. analysis for pure $[NiCl_2(diarsine)_2][ClO_4]_2$, above}. The magnetic susceptibility is given on p. 2603. On storage, the compound gradually became yellow.

Ceric sulphate. The chloride (0·3 g.), dissolved in distilled water (200 ml.), was treated with excess of ceric sulphate dissolved in dilute sulphuric acid, and a deep green precipitate was formed. This was filtered off and dried quickly; it had a formula approximating to $[NiCl_2(diarsine)_2][Ce(SO_4)_3]$ (Found: C, 20·3; H, 4·1. $C_{20}H_{22}O_{12}Cl_2S_3As_4CeNi$ requires C, 21·3; H, 2·9%). The *substance* decomposed when kept and could not be obtained pure. An aqueous solution reacted instantly with perchloric acid to give a deep blue precipitate of the compound obtained by oxidation with nitric acid. When sulphur dioxide was passed into a green solution of the compound, it became first yellow then orange-red.

Dibromodi-o-phenylenebisdimethylarsinenichel(IV) *Perchlorate.*—The finely divided orange tervalent compound, $[NiBr_2(diarsine)_2]Br$ (0·32 g.), was added to 15N-nitric acid (20 ml.) with vigorous stirring; it dissolved to form a deep green solution which was filtered through sintered glass after about 3 minutes. The filtrate was treated immediately with excess of 30% perchloric acid (5 ml.), followed by distilled water (200 ml.), a deep green crystalline precipitate being formed. After about 5 minutes the *perchlorate* (0·3 g.) was filtered off and well washed with distilled water, the last washings having a pale green colour; it was dried *in vacuo* (Found: C, 24·9; H, 3·6; Br, 16·2; Ni, 6·1. $C_{20}H_{22}O_4Br_2Cl_2As_4Ni$ requires C, 24·25; H, 3·2; Br, 16·16; Ni, 5·93%). The analysis shows that the compound could not be obtained as pure as the chloride. The substance is insoluble in organic solvents and is only slightly soluble in water. When treated with sulphur dioxide, the green suspension becomes orange at once owing to reduction. When heated the compound becomes red at about 190° and decomposes above 200°.

The author thanks Mr. H. Terrey and Dr. D. P. Craig for very helpful criticism. The award by the University of London of an Imperial Chemical Industries Fellowship during the tenure of which this investigation was started, is also gratefully acknowledged. He also thanks Professor C. K. Ingold, F.R.S., for his continual interest and advice.

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581. *The Pitting of Zinc by Distilled Water and Dilute Solutions.*

By U. R. EVANS and D. E. DAVIES.

The object of the research was to explain the vertical arrangement of pits produced on zinc by distilled water, to study the corrosion products, and to explain their formation. The vertical alignment is due to corrosion product from an upper pit lodging at points below, and screening them from oxygen; lines of pits can also be set up by the screening action of a polythene thread. A zinc disc whirled in distilled water containing oxygen suffers no pitting. In stagnant water containing oxygen under high pressure, zinc remains unchanged; at ordinary pressure, it becomes pitted. The pits contain white matter and are surrounded by white rings (oriented zinc oxide and some β-hydroxide); further from the pits are films of interference-colour thickness (also oriented zinc oxide), whilst negatively charged colloid particles appear in the liquid. Salt solutions produce a distribution of attack different from that given by distilled water. The results are explained on the theory of oxidation and corrosion advanced by Hoar and Evans.

THE attack produced by distilled water on zinc is slow, even in presence of oxygen; it is, however, localised as pits, and may cause perforation of thin sheet. Bengough and O. F. Hudson

(*J. Inst. Met.*, 1919, **21**, 59) noticed that on cast zinc placed in stagnant distilled water, the pits appeared in straight vertical lines. The arrangement was evidently connected with gravity; a disc of zinc immersed in distilled water contained in a slowly rotating beaker developed a pattern of pits recalling a Catherine wheel; centrifugal force here played the part of gravity.

Evans (*ibid.*, 1923, **30**, 257; *Ind. Eng. Chem.*, 1925, **17**, 363; *J.*, 1930, 486) obtained the same vertical arrangement of pits on rolled zinc. The distribution in distilled water was different from that obtained in sodium or potassium chloride solution. Drops of salt solution placed on a horizontal surface produced attack at their centres, with a broad unattacked zone around the periphery; a ring of zinc hydroxide was formed between the two zones. The results were explained on the basis of differential aeration. The alkali formed at the peripheral (cathodic) zone caused the liquid to spread, so that the area of the drops increased. Drops of distilled water produced attack close to their edges; the white corrosion product formed a crinkled ring which actually touched the periphery at some points, but at others was separated from it by a narrow area free from attack; the main attack occurred just within or below the white ring and, since no alkali was formed, there was no spreading. The presence of carbon dioxide was not needed for attack; water obtained by distillation of dilute sodium hydroxide solution and condensed directly as droplets on the zinc surface caused appreciable corrosion. If much carbon dioxide was present, the attack was considerable, but there was no white corrosion product. The effect of carbon dioxide on the action of distilled and natural water on zinc has been studied in detail by Kenworthy and Smith (*J. Inst. Met.*, 1944, **70**, 463).

E. A. Anderson and Fuller (*Metals and Alloys*, 1939, **10**, 282) found anhydrous oxide on zinc subjected to distilled water free from carbon dioxide, but basic carbonate where the water had contained carbon dioxide. Gilbert (*Sheet Metal Ind.*, 1948, **25**, 2003, 2243, 2441) reported hydroxide when London tap water acted on zinc. Feitknecht and Petermann (*Korrosion u. Metallschutz*, 1943, **19**, 181), studying the attack of zinc chloride solution on zinc, found considerable hydroxide (α-, β-, and ε-forms). In distilled water the inner film was oxide, and the outgrowth β-hydroxide. Feitknecht (private communication, December 21st, 1950) states that he would expect primary zinc oxide round the pits, and that the loose material covering the pits, although originally amorphous or α-hydroxide, might later change into oxide or β-hydroxide.

Not only is the distribution different for distilled water and salt solution, but also the kinetics. Bengough, Stuart, and Lee (*Proc. Roy. Soc.*, 1927, *A*, **116**, 449; 1928, *A*, **121**, 88; 1930, *A*, **127**, 42) showed that fairly concentrated potassium chloride solution attacks totally immersed zinc in presence of oxygen, according to a rectilinear law, the oxygen-uptake V, in time t, being given by $dV/dt = k_1$, whereas the attack by distilled water or very dilute potassium chloride solution was asymptotic, the relation being $dV/dt = k_2(V_\infty - V)$ where V_∞ is the limiting value of V and k_1, k_2 are constants. The rectilinear relation was found to be valid for alloys by Borgmann and Evans (*Trans. Electrochem. Soc.*, 1934, **65**, 249) who used cylindrical rods of zinc or alloy cast in glass. When corrosion was plotted against time, the points fell on straight lines, but the gradient varied. Thus spectroscopically pure zinc was attacked somewhat more slowly than "ordinary" zinc, whereas each alloy corroded at a different rate; iron and, still more so, copper increased the attack on "ordinary" zinc, whereas aluminium diminished it.

Bengough, Stuart, and Lee (*loc. cit.*) noticed that in distilled water and N/10,000-potassium carbonate the curves showed sudden breaks; after the corrosion rate had become negligibly slow, the attack suddenly started again, as though a protective film had disintegrated, and then gradually attack died down. Many such breaks on corrosion–time curves have been reported—for instance during the high-temperature oxidation of copper (Pilling and Bedworth, *J. Inst. Met.*, 1923, **29**, 529) and during the atmospheric attack on aluminium exposed to London air (Vernon, *Trans. Faraday Soc.*, 1927, **23**, 150).

The present paper describes an investigation into the causes of the localised attack, the vertical arrangement of pits, and the character of the corrosion products.

Experimental.

Zinc.—Two grades of zinc sheet (Zn/49, Zn/50) were kindly provided by the British Non-Ferrous Metals Research Association, and slabs of spectroscopically pure zinc by the New Jersey Zinc Company. The compositions are shown in the Table.

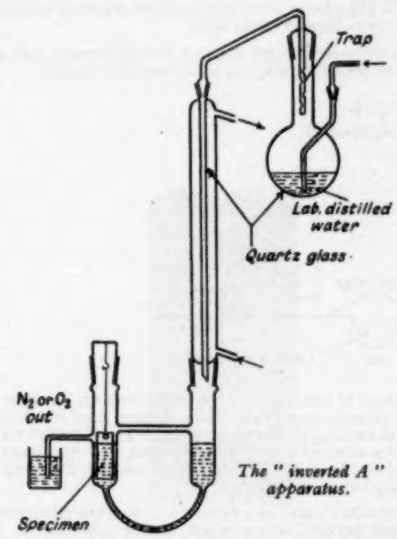
	Zn/49.	Zn/50.		Zn/49.	Zn/50.
Thickness	0·50 mm.	0·48 mm.	Cadmium, % ...	0·002	Trace (<0·002)
Iron, %	0·002—0·003	0·002	Magnesium, %	Not detected	Trace (<0·001)
Lead, %	0·012—0·016	Trace (<0·002)	Tin, %	Not detected	Not detected
Copper, %	0·001	Trace (<0·001)	Aluminium, %	Not detected	Not detected

Many of the experiments were carried out on the " as-rolled " surface, after degreasing; the specimens were alternately immersed in acetone and withdrawn, the liquid film being sucked off with blotting paper before it could evaporate; they then received vapour-degreasing in benzene. In other cases the surfaces were abraded, after degreasing, by use in turn of Oakey's G,F,M,O, 2/0, 3/0, and 4/0, which leaves a very smooth surface; a further degreasing followed.

Both Zn/49 and Zn/50 gave practically the same types and distribution of pitting, and these were the same on a finely abraded as on an " as-rolled " surface. Commercial zinc sheet (" as-rolled " condition) gave somewhat similar pitting. The spectroscopically pure zinc, being rough, could only be used after abrasion, which may have introduced impurites; the same results were obtained.

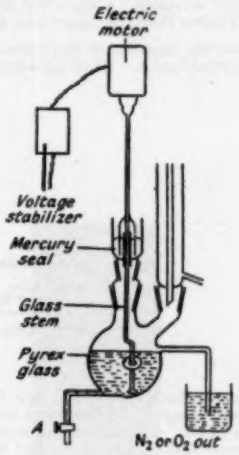
Apparatus.—The distilled water used for the principal experiments was prepared in the laboratory by the further purification of " ordinary " distilled water, previously condensed in glass in a small laboratory still. Subsidiary experiments were carried out with samples of high-quality distilled water kindly provided by other laboratories. All samples gave similar results; the pitting produced by the purest water was more clear cut, the pits being deeper but less numerous than those produced by less pure samples.

FIG. 1.



The " inverted A " apparatus.

FIG. 2.



(Not to scale.)

In view of Kenworthy's demonstration of the effect of traces of copper salts on the corrosion of other materials (*J. Inst. Met.*, 1943, **69**, 67), metals were avoided in designing the still; the redistillation was carried out in an all-quartz apparatus, supplied by the Thermal Syndicate (Fig. 1), the design of the trap being due to Dr. A. E. J. Vickers, who kindly tested the carry-over. It was possible to pass nitrogen (purified by passage through 30% potassium hydroxide solution) through the boiling water, so as to wash out carbon dioxide, before condensation of the steam was started. It was also possible to attach, directly to the outlet, an " inverted A apparatus," which allowed the pH value to be obtained by means of a glass electrode, or alternatively allowed the action on zinc to be studied, without access of air. In general, the vessel was kept full of nitrogen whilst the inverted A apparatus was filling with water. No visible attack on the zinc occurred until oxygen was admitted.

The quartz-condensed water, if allowed exposure to the air, took up a pH of 5·3—5·5; this is close to the value 5·7 calculated for water standing in equilibrium with the amount of carbon dioxide commonly present in the atmosphere. When, by the nitrogen method, the carbon dioxide present in original distilled water was eliminated, a pH value as high as 8 was obtained, suggesting presence of a trace of ammonia. The conductivity varied between 0·07 and $0·2 \times 10^{-6}$ mho cm.$^{-1}$.

Another method of obtaining pure water was to pass " ordinary " laboratory distilled water down a column of mixed resin " Bio-deminrolite F " which replaces the common anions by $(OH)'$ and the common cations by H^{+} (Akeroyd and Kressman, *Chem. Ind.*, 1950, 189); this gave a water of conductivity $0·2 \times 10^{-6}$ mho cm.$^{-1}$ and pH 6·4—6·5. It is not clear how the pH numbers compare with those of samples prepared elsewhere, since most investigators have not quoted pH, but only conductivity.

When it was desired to whirl a disc of zinc under controlled conditions, the apparatus of Fig. 2 was employed (based on that of Evans, " Corrosion of Metals," 1926, p. 108, Arnold). The disc has a central

hole large enough to fit loosely over the glass stem and when there is no rotation rests on the broad foot. During rotation it mounts up the stem, being in contact with glass at only one point at any moment; this point of contact is constantly changing, and there can be no screening from dissolved oxygen.

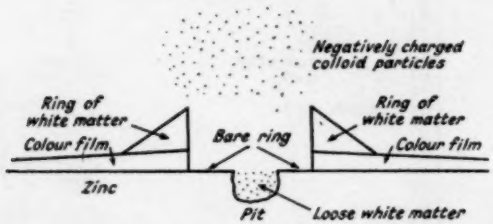
Results.

Vertical Alignment of Pits.—Experiments on partly immersed vertical sheet specimens confirmed the arrangement of pits in vertical lines—somewhat "wavy" unless convection currents were eliminated (Fig. 3). The pits were filled with white corrosion product and were generally surrounded by rings of the white product; the rings around adjacent pits sometimes merged into loops. Outside the white rings, the zinc was unattacked but showed interference colours when viewed by specular reflection; the arrangement of the colours showed the film to be thickest nearest to the pits; contour traces obtained with a Talysurf apparatus appear to confirm this. When the rings of white matter were brushed off, the interference-colour film was found to continue below them (Fig. 4). *X*-Ray studies showed the white product scraped from around the pits to be zinc oxide with some β-zinc hydroxide (identified by a table of spacings kindly provided by Prof. Feitknecht). The white matter obtained from within the pits gave no lines—suggesting that it was amorphous, although the quantity was too small for confident decision. Electron-diffraction studies showed the material responsible for the interference colours to be the anhydrous oxide, with preferred orientation; the white rings also showed orientation. The original "as-rolled" surface was found to carry an anhydrous oxide film without preferred orientation, much thinner than the colour film, as judged from the feebleness of the rings.

After the experiment, the water contained colloidal particles, presumably zinc hydroxide, and gave a good Tyndall cone. Electrophoresis experiments showed that they carried a negative charge.

Fig. 4.

Highly diagrammatic.



In somewhat exceptional cases, the pits were found to follow marks left by the rolling, but in general they were independent of surface blemishes. The arrangement of pits along vertical lines was obtained on "as-rolled" or abraded specimens placed with the rolling or abrasion direction at 45° to the vertical. On hand-polished specimens, the pits were likewise arrayed vertically above one another; transverse abrasion lines made just before immersion remained free from pits. Evidently something dropping from the uppermost pits sets up pitting at points vertically below one another.

When zinc specimens were partly immersed in distilled water in a sloping position, the usual straight lines of pits and loops were obtained on the upper portion, where white matter produced by a pit situated at a high point could slide down the metallic surface until it lodged at some lower point, there producing a fresh pit. On the lower side, where solid matter breaking off from the surface must fall clear of the zinc, the tendency to the linear arrangement of pits was not observed.

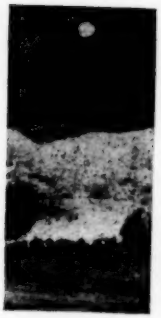
The distribution of attack was affected by impurities in the gas phase. Air purified by sodium hydroxide solution gave pits similar in some cases to those obtained with oxygen; if the purification was omitted, the corrosion extended over vertical streaks bounded by loops of solid white matter. There was then no pitting. This corrosion was probably due to the formation of appreciably soluble zinc hydrogen carbonate, and the phenomenon is probably analogous to the arch-shaped area of corrosion commonly noticed in the early stages when iron or zinc is immersed vertically in sodium or potassium chloride (Evans, *J.*, 1929, 117; Borgmann and Evans, *Trans. Electrochem. Soc.*, 1934, **65**, 258). Along the edges of the arches are walls of membranous iron or zinc hydroxide formed by interaction between the iron or zinc chloride from within and the alkali formed outside.

Production of Pits by Contact with Other Materials.—If the white corrosion product from one pit can set up pitting at a point which otherwise would be immune, other substances might be expected to produce the same effect. Experiments were carried out on totally immersed horizontal specimens around which fibres had been tied or pressed. The fibres used included Polythene (drawn out in the laboratory to a fine thread), glass (similarly drawn out), and linen thread. The elastic character of the Polythene threads allowed them to be brought uniformly into contact with the metal surface over their whole length; thus they set up intense localised corrosion consisting of two parallel trenches or pit-lines, doubtless corresponding to the two crevices on each side of the line of contact (Fig. 5). The linen thread gave less pronounced trenching, whilst glass gave none. The materials may produce specific effects, but the effectiveness of Polythene is probably due to the formation of suitably shaped crevices.

FIG. 3.

Distilled water.

FIG. 7.



M-KCl.

M/75-KCl.

M/100-KCl.

M/500-KCl.

[*To face p.* 2610.

The most reasonable explanation of the intense corrosion at crevices (whether set up by corrosion product or by Polythene) is that the metal, being locally shielded from oxygen, becomes anodic to the main surface. The combination of small anode and large cathode leads, as usual, to intense attack.

Demonstration of the Corrosion Cell.—Since the idea of corrosion currents in liquids of poor conductivty is unfamiliar, it seemed well to study a "model cell" representing the situation at a pit. Helpful discussion with R. May, who has much experience of "model cells," led to the form shown in Fig. 6*a*; the liquid was distilled water. To break down the oxide already present on the lower zinc and thus start anodic attack, an electric current from an external battery was first passed under a current of nitrogen from the lower zinc sheet as anode to the upper zinc as cathode. When this external current was cut off by shifting the double-pole switch from the right-hand position to the left (Fig. 6*b*), the current started to flow back through *M*, with the lower zinc as cathode; this merely represented the usual behaviour of a polarised system, being analogous to the discharge of an accumulator. The back-flow current dropped to zero in about 3 hours, and in experiments under nitrogen no current was produced in the opposite direction. If, however, the nitrogen was replaced by oxygen soon after the

FIG. 5.

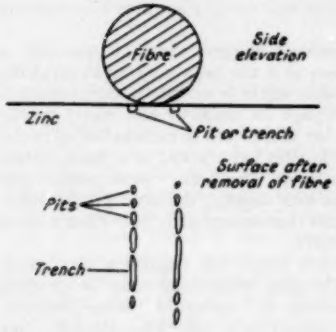
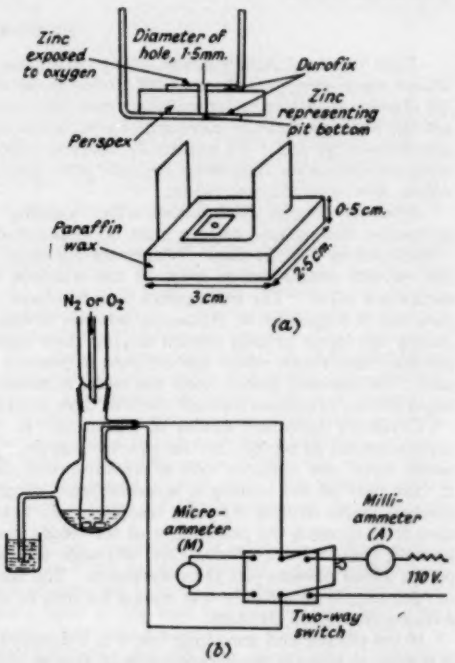


FIG. 6.



polarising current had ceased to flow, then a current in the forward direction was obtained, the bottom zinc acting as anode and the upper (aerated) zinc as cathode. The current became constant after a few hours at a value varying in different experiments from 0·5 to 1·5 microamperes. The experiments suggest that a corrosion current can continue to flow through distilled water under geometrical conditions similar to those existing during the pitting of zinc.

Experiments with Eccentric Whirler.—If the pitting or trenching set up by contact with zinc oxide particles (or with Polythene thread) is really due to local screening from oxygen, it would seem possible to prevent intense attack by maintaining an oxygen supply at all points on the surface, with the eccentric whirler (Fig. 2). A zinc disc whirled in distilled water with oxygen above the water surface remained free from pitting or any visible change; under stagnant conditions, experiments, carried out in the same apparatus containing the same water and the same oxygen, produced pitting, whether the zinc was totally or partly immersed. A small and rather variable concentration of zinc was detected in the water under whirling conditions, but this showed no tendency to increase beyond about 10^{-5} g.-ion/l.; the estimation was carried out in a Spekker apparatus by a method due to Mayne and Noordhof (unpublished work) based on sodium diethyldithiocarbamate. The loss of weight of the zinc at the end of 4 days was about 0·0008 g.—similar to that found in the water after whirling, namely 0·00065 g.

Experiments under Pressure.—Even under stagnant conditions, oxygen under pressure (10 atmospheres, decreasing to 7 atmospheres during the experiment) prevented pitting. This was shown by experiments in glass vessels enclosed in a stainless steel "bomb." Bengough and Wormwell's method (Report Chem. Res. Board 1935—1937, H.M.S.O., 1938, p. 17) was used, the high-pressure oxygen being introduced before the water; when the water was introduced before the pressure was raised, pitting occurred.

Experiments in Chloride Solutions of Different Concentrations.—Zinc was tested in potassium chloride solutions of concentrations 2·0, 1·0, 0·2, 0·1, 0·02, 0·01, 0·002, 0·001, 0·0002, 0·0001, 0·00002, and 0·00001M. In one series, plates were partly immersed in the solutions; in another, drops of solution were placed on horizontal plates. Well below 0·01M., the distribution somewhat recalled that produced by distilled water, with numerous pits surrounded by loops; at many points the corrosion product reached the water-line (in partial immersion experiments) or the drop margin (in drop experiments). Well above 0·01M., there was a continuous unattacked area below the water-line or around the drop periphery; this area showed high-order interference tints, indicating a film thickest near the water-line; electron diffraction identified the film as oriented zinc oxide. Round about 0·01M., both types of attack were found at different places. The situation is shown in Fig. 7. Sodium chloride and potassium sulphate gave similar results.

Discussion.

Facts requiring Interpretation.—Any satisfactory mechanism must explain: (1) absence of attack when oxygen is absent; (2) pitting under stagnant conditions when oxygen is present; (3) absence of pitting under whirling conditions even though oxygen is present; (4) preferential pitting where particles of corrosion product settle or at contact with thread; (5) loose oxide and ε-hydroxide in pits; (6) negatively charged colloidal particles in liquid; (7) colour film of oriented zinc oxide thickening towards pits; and (8) white zinc oxide also oriented overlying colour film in its thickest region.

Effect of Oxygen Distribution.—The whirling experiments suggest that, to maintain a protective film on zinc, oxygen must be replenished as soon as it has been used up in repairing "weak points" of the film. When whirling stops, corrosion starts at certain points, although the oxygen concentration must at the moment of stoppage be uniform and equal to the saturation value. The weak points may be places where the film is rich in defects owing to the presence of impurities or broken by internal stresses; if the film has cracked at a point, it will during the repair process remain thinner there than elsewhere. The term "weak point" will include other places where the outward movement of zinc ions through the film is abnormally easy; for instance, places where the metal is disarrayed and thus energy-rich, providing a more rapid stream of cations through the film than occurs elsewhere.

Evidently there are grades of weakness. A very weak point will require a very rapid replenishment of oxygen for its effective repair. A moderately weak point may be repaired easily under the ordinary rate of replenishment characteristic of "unstirred" water, but not if that part of the surface is screened from oxygen by means of a Polythene thread. But shielding from oxygen, however complete, will not of necessity produce corrosion. All that it does is to increase the probability of corrosion; within a shielded region, there will in general be both pits and uncorroded zinc, although the shielding is, at the outset, no greater at the points which develop pits than elsewhere. The fact that the probability of attack increases as oxygen supply diminishes was shown for iron in distilled water by Mears and Evans (*Trans. Faraday Soc.*, 1935, **31**, 530).

If the pitting and trenching below a Polythene thread is attributable to oxygen-shielding, it is easy to explain the arrangement of pits on different surfaces. On a vertical surface, the corrosion product formed at a pit near the top will fall by gravity; if particles lodge at points on the surface, they will diminish the possible replenishment rate for oxygen so that minor weak points—which would not develop pitting on an unshielded surface—will become the sites of pits; hence the arrangement in vertical lines. This cannot happen on a horizontal surface; hence the original pits will not give birth to others. Nor can it happen on the lower side of a sloping plate; on the upper side particles can slide downwards and the lines of pits are again obtained.

Electrochemical Action around a Weak Point.—Imagine a horizontal zinc surface carrying an oxide film and placed in water containing dissolved oxygen; imagine that the main part of the film is sound but that one weak point exists, through which zinc cations can move outwards (also electrons, since the defects which permit movement of ions usually favour movement of electrons). If the rate of replenishment of oxygen in the liquid is good, there will always be a layer of absorbed oxygen *atoms* on the outer surface, which can be converted into *ions* by the electrons moving outwards; consequently the zinc cations as they arrive at the outer surface

can take up their places between the oxygen anions, giving an extra layer of zinc oxide. Thus, the film locally thickens, by accretion on the outside—a mechanism precisely similar to that demonstrated by Wagner (*Z. physikal. Chem.*, 1933, *B*, **21**, 25) for the formation of oxide-films on *dry* metal; the thickening at the weak spot continues until the increased thickness reduces the rate of movement of cations outwards, in other words until the spot has ceased to be exceptionally weak; pitting is avoided.

If the liquid contains no oxygen, the emerging cations can enter the liquid, becoming hydrated. However, this would soon leave the metal negatively charged, and the escape of cations must then cease (except in so far as the charge can be balanced by the deposition of hydrogen ions at points around, which can probably be neglected owing to the high over-potential of zinc). Again, there is no pitting.

If the maximum rate at which oxygen can be replenished is insufficient to arrest the zinc ions as they emerge, but is sufficient to provide adsorbed oxygen atoms at the area of sound film surrounding, and *very* close to, the weak spot, then the excess of electrons left behind when the cations enter the liquid may serve for the reduction of the oxygen. In other words, electrochemical reactions are set up which may tentatively be written thus:

at the weak spot (anodic)	$Zn = Zn^{++} + 2e$
on the sound film (cathodic)	$O_2 + 2H^- + 2e = H_2O_2$

Since the number of cations produced is equal to the number destroyed, there are no unbalanced ions. The hydrogen peroxide could be reduced to water by further cathodic action, but since hydrogen peroxide has been detected in fairly large amounts in the action of distilled water on zinc or other metals (Traube, *Ber.*, 1882, **15**, 2441; Churchill, *Trans. Electrochem. Soc.*, 1939, **76**, 341; Delahay, *J. Electrochem. Soc.*, 1950, **97**, 198), the second step does not seem to be complete.

Once zinc cations have accumulated in the liquid and reached the cathodic area, a different cathodic reaction becomes possible. The adsorbed oxygen atoms are converted into ions by the electrons, and the zinc cations arriving from the anode take their places between them, giving fresh layers of zinc oxide, as identified by electron diffraction. This formation of zinc oxide differs from the ordinary oxidation in air in that cations arrive *from the outside*. Thus, provided that electrons can move easily through the film, there is no reason why the thickening rate should fall off with time. It now becomes apparent why the oxide film reaches interference colour thickness, which is not generally reached in ordinary oxidation processes except at elevated temperatures. Apparently the film resembles high-temperature oxide films in being under internal stress and breaks up when a certain critical thickness is reached (Evans, *Trans. Electrochem. Soc.*, 1947, **91**, 547), forming the loose white rings which overlie the colour films where they are thickest; the fact that the white matter of the rings shows the same preferred orientation as the colour rings indicates that it is formed by the break-up of the film and not dropped from the liquid.

When the liquid contains many zinc ions, they are presumably balanced by hydroxyl ions (the equivalent removal of hydrogen having taken place at the cathode). The solubility of zinc hydroxide (and oxide) is low, and sooner or later the liquid will become supersaturated. It has been shown by Aebi (Diss., Berne Univ., 1946, p. 10) that the least soluble (*i.e.*, most stable) of the possible phases is the ε-hydroxide, but that frequently a metastable phase is first deposited. Whichever compound is first precipitated, the particles, whilst still of colloidal size, apparently acquire a negative charge by adsorbing hydroxyl ions and thus become stabilised. They migrate by electrophoresis towards the anode and are presumably deposited; this may explain the loosely adherent white matter (probably amorphous) found in the pits.* It is only partially protective—as would be expected—but after a time the anodic attack is stifled, which explains the asymptotic corrosion–time curve established by Bengough, Stuart, and Lee (*loc. cit.*)—in contrast with the straight lines obtained in chloride solutions where both anodic and cathodic products are soluble, zinc hydroxide being formed when they meet. Thus the difference in the location of corrosion products, as well as in the character of the corrosion–time equation, is explained.

Electrochemical Action in Badly Conducting Liquids.—A necessary condition for electrochemical action in badly conducting solutions is that *very small* anodic areas shall be surrounded by annular cathodic areas; only in that case can a cathodic area (much larger than the anodic area) exist very close to the anode, keeping the electrolytic resistance small. In general, the

* The white matter in the pits might also be due to anodic discharge of hydroxyl ions.

ratio of effective cathodic area to anodic area determines the intensity of attack, which explains the sharp pitting produced by distilled water (especially the purest distilled water) on zinc. In more concentrated (and better conducting) solutions the total corrosion is greater but the attack less intense. Any doubts about the possibility of a zinc–oxygen cell with distilled water as electrolyte are dispelled by the experiments with the model cell.

The explanation suggested for the behaviour of zinc in distilled water fits the general picture of corrosion and passivity put forward by Hoar and Evans (Electrochem. Soc. Spring Meeting, 1951). The same picture explains why alloying additions (*e.g.*, chromium and aluminium) which confer resistance to high-temperature oxidation also prevent wet corrosion. The mechanism now put forward for zinc has points in common with that suggested for tin by Brennert (Techn. Publ. Int. Tin Res. and Dev. Council, D. No. 2, 1935) and Hoar (*Trans. Faraday Soc.*, 1937, **33**, 1152).

Subsequent Breakdown of Films.—If the solid product formed both at cathodic and anodic areas is anhydrous zinc oxide, the system is metastable, since the ε-hydroxide is less soluble. If once a nucleus of hydroxide appears, presumably recrystallisation will quickly spread and the whole film may become non-protective. This may be the cause of the sudden recommencement of the corrosion of zinc in distilled water, after it has become very slow, as noted by Bengough, Stuart, and Lee (*loc. cit.*).

Concentration of Zinc reached in the Whirler Experiments.—According to Feitknecht and Häberli (*Helv. Chim. Acta*, 1950, **33**, 929) the solubility products $[Zn^{++}][(OH)^-]^2$ are as follows:

Amorphous $Zn(OH)_2$	$3{\cdot}9$—$5{\cdot}5 \times 10^{-16}$
α-$Zn(OH)_2$	$1{\cdot}4 \times 10^{-16}$ (Aebi, *loc. cit.*).
β_1-$Zn(OH)_2$ *	$5{\cdot}0$—$6{\cdot}0 \times 10^{-17}$

ε-$Zn(OH)_2$, the stable form, has naturally a still lower value; Feitknecht (private communication, July 28th, 1950) gives this as $2{\cdot}7 \times 10^{-17}$ if calculated on conventional principles, and $8{\cdot}4 \times 10^{-18}$ if the Debye–Hückel equation is used.† Aebi assigns to the anhydrous oxide a value 7×10^{-17}, corresponding to the equilibrium ZnO (solid) + $H_2O \rightleftharpoons Zn^{++} + 2OH^-$. If 1×10^{-16} is taken as a basis of calculation and it is noted that the water assumes a pH value of 8·5 after the whirling experiment, or a pOH value of 5·5, then it is evident that, if the water becomes saturated with zinc oxide (or α-hydroxide), it should contain $10^{-[16-(2\times5{\cdot}5)]} = 10^{-5}$ g.-ion/l. of zinc, in agreement with experiment. If, however, the stable ε-hydroxide was being deposited, with a solubility product of about 10^{-17}, the agreement would be poor. Actually, since electron diffraction indicates the anhydrous oxide, the results are explained.

We thank Dr. J. W. Menter for fruitful co-operation in the electron-diffraction work, Dr. W. H. Taylor and Mr. G. J. Dickins for facilities in connection with the *X*-ray studies, and Prof. W. Feitknecht for valuable information regarding diffraction patterns of numerous compounds. One of us (D. E. D.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant.

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University of Cambridge.

[*Received, May 10th*, 1951.]

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* Feitknecht (*Helv. Chim. Acta*, 1949, **32**, 2294) states that the two forms of β-$Zn(OH)_2$ known as β_1 and β_2 give *X*-ray patterns differing only in intensity.

† The difference between the two values may cause surprise, and the reader is referred to the discussion of the matter by Feitknecht and Häberli (*Helv. Chim. Acta*, 1950, **33**, 922, especially pp. 930, 931). For the present purposes the question is not important, since no calculations in this paper are based on the solubility product of ε-hydroxide.

582. *Adsorption and Swelling Experiments with an Amine-type Ion Exchanger.*

By C. W. Davies and T. G. Jones.

The behaviour of the resin Amberlite IR-4B has been studied in aqueous solutions of hydrochloric acid, with and without the addition of added chlorides. The measurements enable the uptake of water by the ionised resin to be calculated, and it is shown that it corresponds to little more than a monolayer. This knowledge of the water adsorption enables the adsorption of acid to be correctly calculated, and the results are compared with the equations of Bishop and Bauman. A new equation is proposed which better represents the ionisation equilibrium.

It is found that a regenerated basic resin normally contains significant amounts of carbonate. This exchanges with the anions of added neutral salts, and also complicates the determination of the moisture content of the resin.

The uptake of acid by amine-type ion-exchange resins has been studied by a number of authors. It is convenient to describe the process as one of adsorption, but it is generally agreed that the mechanism is given by one or other of the following equations :

$$(a)\ \mathrm{R{\cdot}N} + \mathrm{H^{\cdot}} + \mathrm{A'} \rightleftharpoons \mathrm{R{\cdot}NH^{\cdot}} + \mathrm{A'}, \text{ or}$$

$$(b)\ \mathrm{R{\cdot}NH{\cdot}OH} + \mathrm{H^{\cdot}} + \mathrm{A'} \rightleftharpoons \mathrm{R{\cdot}NH^{\cdot}} + \mathrm{A'} + \mathrm{H_2O}$$

where A′ is an acid anion, N is the nitrogen of a primary, secondary, or tertiary amino-group, and R represents the remainder of one chemical equivalent of the resin. Although there has been some discussion as to which of these is the more appropriate, they are for most purposes equivalent, as are the corresponding formulations for a simple monomeric base.

The data so far available, mostly presented graphically, give a general picture of the behaviour of the amine resins, but do not provide a basis for a quantitative study of the dissociation equilibrium. Our object was to obtain results which could be utilised for this purpose, and we have therefore studied the system Amberlite IR-4B–hydrochloric acid–water as accurately as possible, paying special attention to reproducibility, moisture content, and the correct formulation of acid adsorption by a swollen resin.

Experimental.

Materials.—The resin used for this work was a sample of "Amberlite IR-4B A.G.," made by the Rohm & Haas Co. of Philadelphia. It contained considerable quantities of carbonate and sulphate. When the latter was removed by alternate treatments with 0·1N-hydrochloric acid and 0·1N-sodium hydroxide the measured acid adsorption in successive cycles was found to be 6·43, 7·20, 6·94 milliequivs. per g. The increase after one alkali treatment was due to the removal of sulphate, but the subsequent decrease was real. Heating of the solid resin, *e.g.*, for moisture determination, also led to a decrease of adsorptive capacity. Sodium carbonate and sodium hydrogen carbonate, when used as regenerants, caused similar but smaller decreases in capacity. The resin imparted a yellow colour to sodium hydroxide solutions, and to neutral and acid solutions when hot, and all solutions after contact with resin gave a greenish-yellow colour with Nessler's solution. Contact with acid for some hours at 60° appears to cause considerable breakdown of the cross-linked resin structure. Swelling becomes excessive and the mechanical strength of the resin particles is permanently lost. These results show that a resin intended for quantitative work must be thoroughly aged, and even then results may not be exactly reproducible unless a single batch of resin is used throughout.

Treatment of the resin with 0·1N-sodium hydroxide caused a loss of 2—3 milliequivs. of alkali per g. of resin, presumably through salt formation at phenolic groups. Very prolonged washing was required to remove the alkali gradually liberated when these groups hydrolyse.

For the experiments reported later, a large batch of resin was prepared by thorough treatment with 2% sodium carbonate, followed by washing with distilled water until the specific conductivity had fallen to 2×10^{-4} ohm^{-1} cm.$^{-1}$. For particle-size experiments, part of this air-dried material was ground, and, after being kept for a few days in water, was wet sieved, and fractions of 20/40, 40/60, 60/80, and 80/90 mesh size were collected and thoroughly washed.

Determination of Moisture.—The air-dried resin contains 25—30% of water and, as this figure was required accurately, the following methods of moisture determination were tried: (*a*) prolonged evacuation over phosphoric oxide at room temperature; (*b*) heating at atmospheric pressure to 130°; (*c*) heating to intermediate temperatures in a vacuum-oven; and (*d*) entrainment in AnalaR light petroleum, b. p. 100—120°, in a standard Dean and Stark apparatus (Tate and Warren, *Analyst*, 1936, **61**, 367). In the first method, the greater part of the water is lost fairly rapidly, especially by the resins

of smallest particle size, but a slow loss continues for a very long time; in an experiment with 20/40 mesh resins, the loss after 1 day was 88·5%, after 1 week 94·2%, after 1 month 97·5%, and after 2 months 99·2% of the total loss recorded after 4 months' treatment. Method (*b*) gives a considerably greater loss of weight than method (*a*), and, as will be shown later, the additional volatile matter consists of carbon dioxide. In method (*c*) an initially rapid loss of weight is succeeded by a further slow loss during several days. When the % loss in weight is plotted against time, the steep curve obtained over the first few hours passes rather abruptly into a linear portion, the slope of which is steeper the higher the temperature. It is believed that this linear portion represents loss of carbon dioxide, for when it is continued back to zero time the extrapolated loss agrees with that obtained by method (*a*). Method (*d*) also gives values agreeing with method (*a*) within the accuracy, of about 3%, obtainable by the distillation method. The concordance between the results of methods (*a*) and (*d*) and the extrapolated values from (*c*) satisfied us that they led to a correct value for the moisture content of the resin, in spite of the higher value obtained by the other procedure, and a further examination of method (*b*) is described in the next section.

Determination of Carbonate.—The moisture content of six samples of a uniform batch of resin was determined by evacuation at room temperature. The variation was very small, and the mean loss after 124 days was 24·94%. For a further six samples heated at 130° for 3 days the mean loss was 30·47%. If the difference is ascribed to carbonic acid, it implies the presence of 2·4 milliequivs. of carbonate per g. of dried resin. The dried samples were then given prolonged contact with 0·1N-carbon dioxide-free sodium hydroxide, and the solutions subsequently examined; the unheated samples clearly showed the presence of carbonate. Indicators cannot be used with heated samples owing to the pronounced colour of the solutions, but potentiometric titrations against hydrochloric acid showed carbonate to be present in the unheated, and absent from the heated, samples. The amount of carbonate found by analysis for the unheated samples was 2·2 milliequivs. per g., which agrees reasonably well with the calculated figure. Further experiments gave 1·88 milliequivs. of carbonate present after 13 days in a vacuum-oven at 70°, and a definite trace after further prolonged treatment at 110°, so it is clear that a temperature of at least 120—130° is necessary for the complete removal of carbonate in a reasonable time.

A further check on the carbonate of the resin is provided by the loss in weight occurring when the resin is equilibriated with hydrochloric acid solutions. This figure, obtained repeatedly in the course of later work, agreed well with the calculated figure of 2·4 milliequivs. per g. The most convenient method of moisture determination, which we finally adopted, was therefore to determine the total loss in weight at 130° and to calculate the moisture content by subtracting the known figure for the carbonate content of the resin.

Experiments with Neutral Salt Solutions.—Preliminary experiments showed that reaction occurred when neutral salt solutions were added to the prepared resin. With silver nitrate there was some reduction; with sodium chloride the solution became alkaline and lost chloride; and with barium chloride there was copious precipitation.

Quantitative experiments were carried out with sodium chloride. 100 Ml. of the solution were left in contact, in flasks with closely fitting ground-glass stoppers, with a weight of resin corresponding to 1 g. of the dry material. After 7 days, with intermittent shaking, 50 ml. of the solution were withdrawn through a sintered-glass filter and analysed for total alkalinity. The results are in Table I.

TABLE I.

NaCl, g.-equiv./l.	0	0·02	0·10	0·20	1·00
Milliequiv. of alkali released/g. of dry resin	0·02	0·21	0·41	0·63	1·15

The only anions, other than chloride, found in the solution after contact were carbonate and bicarbonate. The concentrations of each were determined for the 0·20N-solution as follows. More than sufficient sodium hydroxide (e_1 milliequivs.) to convert the bicarbonate into carbonate was added to 50 ml. of the solution, and after being heated to boiling and addition of 2 ml. of 10% barium chloride, the solution was rendered colourless to phenolphthalein with hydrochloric acid (e_2 milliequivs.). An excess of acid (e_3 milliequivs.) was added to dissolve the barium carbonate, and after the carbon dioxide had been boiled off the solution was titrated with sodium hydroxide and use of bromocresol-purple (e_4 milliequivs.). The bicarbonate, $2(e_1 - e_3)$, was found to be 0·50 milliequiv./g. of dry resin, and the carbonate, $2(e_3 - e_4) - 2(e_1 - e_2)$, was 0·13 milliequiv. 1·57 Milliequivs. of carbonate were extracted from the wet resin after the experiment.

Experiments with Hydrochloric Acid Solutions.—A large quantity of resin (batch A, 20/40 mesh) was weighed out at one time into 1-g. samples, some of which were used during the course of the work for periodic moisture determinations. In making a measurement of the apparent adsorption of hydrochloric acid by the resin, 100 ml. of acid of suitable concentration were added from a calibrated pipette to a numbered bottle with closely fitting stopper. The weighed portion of resin was added, and the contents of the bottle mixed by careful swirling two or three times a day. After 14 days the solution was transferred to another dry bottle, and aliquots were titrated against carbonate-free sodium hydroxide with bromocresol-purple as indicator. Just before the end-point the solution was boiled for 2—3 minutes, and cooled while protected from carbon dioxide. The alkali was standardised by potassium hydrogen phthalate dissolved in boiled-out water, and also, *via* hydrochloric acid, by recrystallised borax.

Considerable carbon dioxide was lost during the adsorption experiments, and the loss in weight of the bottles agreed with that calculated from the carbonate determinations. Control bottles treated in the same way, but containing no resin, showed no loss of weight and no change in concentration. Experiments on the rate of adsorption showed that equilibrium was attained within 7 days for 20/40-

mesh resin and in considerably shorter periods with the finer fractions. However, a constant time of 14 days was allowed. The results are in Table II, where the first line gives the concentration of acid at equilibrium in g.-equivs./l. The four values for the adsorption of hydrochloric acid, in milliequivs., are discussed later. It may be noticed that all show a maximum.

TABLE II.

Adsorption of HCl *by resin (Batch A).*

$C \times 10^3$	3·72	20·01	64·5	112·8	411·4	914	1938
X_1, Eqn. 1 *	5·63	6·42	6·83	7·04	7·46	7·52	7·45
X_2, Eqn. 2 *	7·63	8·71	9·26	9·55	10·11	10·20	10·10
X_3, Eqn. 3 *	7·63	8·70	9·24	9·50	9·95	9·87	9·41
Γ^1_{HC}, Eqn. 6 *	7·63	8·70	9·25	9·52	10·03	9·99	9·71

* See p. 2619.

The above results do not give full information about the state of the system, as will be shown later, and further series of measurements were carried out with hydrochloric acid and added chlorides, in which all analyses referred to known weights of solution, and in which the chloride was determined gravimetrically in addition to loss of acidity. Preliminary measurements showed that the resin was chloride-free, and that in the absence of added chlorides the determination of free acid and of chloride gave identical results (cf. Table IV, line 1). The determination of chloride followed the details given by Keenan, McLeod, and Gordon (*J. Chem. Physics*, 1945, **13**, 466). All analyses were in duplicate (at least), and agreed to 1 part in 3000 parts. Resin from a different batch, though conditioned in the same way, had to be used for these series. Periodical moisture checks were made as before. The results are in Tables III and IV, which give the mean of concordant duplicates, all concentrations being in g.-equivs./kg. of solution. The added salt was sodium chloride in every case except the one marked with an asterisk in Table IV.

TABLE III.

Original HCl *concn. approx.* 0·134N. *Batch B resin. Dry weight of resin samples,* 1·012 *g.*

Nos.	Wt. of soltn. (g.).	Moisture in resin (g.).	Original concns.: acid.	Original concns.: chloride.	Equilibrium concns.: acid.	Equilibrium concns.: chloride.
1, 2	99·85	0·217	0·12940	—	0·04440	—
3, 4	100·05	0·216	0·12905	0·17934	0·04255	0·09360
5, 6	100·72	0·218	0·12818	0·32660	0·04037	0·24165
7, 8	103·90	0·230	0·12553	1·0858	0·03714	1·0064
9, 10	107·74	0·230	0·12219	1·9730	0·03439	1·8985
11, 12	114·88	0·223	0·11563	3·5658	0·03023	3·4985

TABLE IV.

Original HCl *concn. approx.* 0·20N. *Batch B resin. Dry weight of resin samples,* 1·012 *g.*

Nos.	Wt. of soltn. (g.).	Moisture in resin (g.).	Original concns.: acid.	Original concns.: chloride.	Equilibrium concns.: acid.	Equilibrium concns.: chloride.
13, 14	100·04	0·215	0·2061	0·2061	0·1175	0·1175
15, 16	100·85	0·215	0·2036	0·4010	0·1135	0·3136
17, 18	107·75	0·215	0·1909	2·0232	0·1009	1·9464
19, 20	114·88	0·215	0·1784	3·6140	0·09116	3·5450
21, 22 *	111·87	0·214	0·1837	1·3708	0·09846	1·2968

* Added salt $BaCl_2$. These solutions were also analysed for barium (as $BaSO_4$) before and after contact with the resin. Original and equilibrium concentrations of barium were 1·1822 and 1·1952, respectively.

TABLE V.

No.	Wt. of soltn. (g.).	Moisture in resin (g.).	Acid concns.: original.	Acid concns.: equilibrium.	NaCl concn.
23	100·73	0·231	0·6144	0·5243	0
24	101·14	0·231	0·6131	0·5224	0·0989
25	102·69	0·231	0·6023	0·5118	0·487
26	104·68	0·231	0·5971	0·5059	0·955
27	108·42	0·231	0·5748	0·4844	0·1847
28	101·43	0·230	1·0101	0·9211	0
29	102·23	0·230	0·9968	0·9070	0·1957
30	105·10	0·230	0·9319	0·8421	0·9515
31	103·01	0·219	1·8778	1·7938	0
32	103·73	0·220	1·8607	1·7761	1·1925
33	106·73	0·219	1·8091	1·7252	0·9372

Some further measurements with the same batch of resin were made at higher concentrations of acid, and the results are in Table V. These solutions were not analysed for chloride.

Discussion.

Our preliminary results need not be discussed in detail, since they agree in most respects with much that has been published since this work began (Kunin and Myers, *J. Phys. Colloid Chem.*, 1947, **51**, 1111; *J. Amer. Chem. Soc.*, 1947, **69**, 2874; "Ion Exchange," Ed. F. C. Nachod, Academic Press, N.Y., 1949, pp. 23, 62). Thus, it is widely agreed that the adsorption of acid by a weak base resin (or, in general, the ionisation of a resin containing weak acid or basic groups) is a much slower process than that of ion exchange. Reduction of particle size greatly accelerates the process without affecting the capacity of the resin. The reduction in capacity that we observed on heating the air-dried resin deserves emphasis, since it means that moisture determinations involving heating must be carried out on separate samples of resin not used for other purposes. Our results indicated that the heating affected in some way the linking of some of the basic groups, since no material (other than water and carbon dioxide) appeared to be lost, either during the heating or on subsequent extraction with water.

The high carbonate content of a basic resin that has been regenerated with sodium carbonate has not been reported before. It is usually assumed that the carbonate radical is lost by hydrolysis during washing (Duncan and Lister, *Quart. Reviews*, 1948, II, 327). Apart from the fact that the carbonate must be allowed for in any accurate study of acid adsorption, it has a very important bearing on both moisture determination and the question of "salt splitting" by a basic resin. To remove all water from a resin by evacuation over phosphoric oxide requires several months; whereas heating the resin leads to a slow loss of carbon dioxide which is not completed in a reasonable time at temperatures under about 130°. Heating to constant weight at 110°, which Duncan and Lister (*loc. cit.*) quote as the customary procedure, would have required several weeks with our resin samples.

Salt Splitting.—The possibility of anion exchange between a free base resin and a neutral salt has been discussed by several writers (cf. earlier refs.). Kunin and Myers, who regenerated their Amberlite IR-4 with sodium hydroxide, found a very slight degree of exchange, some of the added ion being taken up by the resin, and the pH of the solution becoming greater than 7. This result is usually taken as evidence that the resin contains free hydroxyl groups which are available for exchange, but the nature of the material, and the results themselves, suggest that the degree of ionisation of the resin is only very small.

With a carbonate-treated resin, anion exchange can be very considerable, as is shown by the results in Table I. A quantitative treatment of these data is rendered difficult by the simultaneous presence of bicarbonate and carbonate radicals, as well as chloride; but they strongly suggest an exchange between chloride and bivalent carbonate ions, preferential adsorption being shown by the resin, as would be expected, for the bivalent radical. For instance, when 0·20N-sodium chloride was equilibriated with 1 g. of the resin, the ultimate distribution of the chloride radical was 0·63 milliequiv. in the resin phase and 19·37 milliequivs. in the solution, whereas the corresponding figures for the carbonate radical were 1·57 in the resin and 0·63 in the solution. Even in 1N-sodium chloride only one-half of the carbonate is exchanged, and not the 90% or more that would be expected for a normal uni-univalent exchange. This is strong evidence that the carbonate is present on the resin as bivalent ions, and a theoretical argument pointing in the same direction is that at the surface of the positively charged resin the electrical field will greatly favour the right-hand side of the equilibrium $HCO'_3 \rightleftharpoons H^{\cdot} + CO_3''$, as compared with conditions in the solution.

From our results with different batches of resin it would appear that Amberlite IR-4B, after regeneration with sodium carbonate and prolonged washing, will always contain 2·2—2·4 milliequivs. of carbonate per g., and for this reason will show extensive exchange with neutral salts. Even a resin regenerated with sodium hydroxide would tend to acquire an appreciable carbonate content through preferential adsorption, unless rigorous precautions against carbon dioxide were taken during regeneration, washing, and air-drying. Kunin and Myers (*loc. cit.*) determined the amount of anion exchange by titrating the alkali released from the resin with phenolphthalein as indicator. As this would not detect bicarbonate resulting from anion exchange followed by hydrolysis, it is possible that appreciably more anions were taken up by their resin than their results would indicate.

Adsorption of Acid.—Previous authors who have reported on the adsorption of acids by basic resins (Bhatnagar *et al.*, *J. Indian Chem. Soc.*, 1939, **16**, 249, 261; 1940, **17**, 361; Akeroyd and Broughton, *J. Physical Chem.*, 1938, **42**, 343; Schwartz, Edwards, and Boudreaux, *Ind. Eng. Chem.*, 1940, **32**, 1462; Kunin and Myers, *loc. cit.*; Bishop, *J. Phys. Colloid Chem.*, 1946, **50** 6; 1950, **54**, 697) appear to have all used volumetric procedures. For instance, *v* ml. of

nM-hydrochloric acid are put in contact with a known weight of air-dried resin composed of r g. of dry resin and w g. of water. If at equilibrium the solution is found to be m molar, the hydrochloric acid adsorbed per g. of (air-dried) resin may be given as

$$X_1 = (n - m)v/(r + w) \text{ milliequivs.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

It is not always clear in the literature whether the water content of the resin has been allowed for. If the moisture content is known, the adsorption of acid may be reported as

$$X_2 = (n - m)v/r \text{ milliequivs.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Equation (2), however, does not allow for the diluting effect of the water introduced with the resin. If this is assumed to form part of the solution at equilibrium, then $(v + w)$ ml. of this solution contain $(v + w)m$ milliequivs. of hydrochloric acid and the amount adsorbed per g. of dry resin is given by

$$X_3 = [nv - (v + w)m]/r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Equations (2) and (3) involve tacit assumptions as to the distribution of the water in the system, and differ for this reason. Moreover, neither makes allowance for the changing density of the solution. A correct expression for the adsorption of acid (and of water, to be discussed later) is derived as follows. $(r + w)$ G. of moist resin are treated with vd g. of nM-hydrochloric acid, of density d. This solution contains $nvM/1000$ g. of hydrogen chloride (M = molecular weight) and $v(d - nM/1000)$ g. of water. The equilibrium solution is found to be m-molar, and its density is d'. If its volume is v', it contains $mv'M/1000$ g. of hydrogen chloride and $v'(d' - mM/1000)$ g. of water. Writing the composition of the resin phase as (r g. of resin + $r\Gamma^{g}_{H_2O}$ g. of water + $r\Gamma^{g}_{HCl}$ g. of hydrogen chloride) we therefore have:

$$\Gamma^{g}_{H_2O} = \frac{v(d - nM/1000) + w - v'(d' - mM/1000)}{r}$$

and

$$\Gamma^{g}_{HCl} = (nv - mv')M/1000r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

If the adsorption of hydrogen chloride is expressed in milliequivs. per g. of dry resin

$$\Gamma_{HCl} = (nv - mv')/r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The volume v' in these expressions is not accessible to direct measurement, and any evaluation of Γ_{H_2O} and Γ_{HCl} must depend on some assumption regarding the position of the boundary between the two phases. If we assume, as in equation (3), that the adsorption of water is zero, then on this arbitrary convention we have:

$$v'(d' - mM/1000) = v(d - nM/1000) + w$$

and substituting for v' in the expression for the adsorption of hydrogen chloride

$$\Gamma^{1}_{HCl} = \frac{1}{r}\left[nv - \frac{m\{v(d - nM/1000) + w\}}{(d' - mM/1000)}\right] \quad . \quad . \quad . \quad . \quad . \quad (6)$$

This differs from equation (3) in containing, as correction factors, the weights of water in 1 ml. of the initial and final solutions, respectively.

The four equations (1), (2), (3), and (6) are applied to one series of measurements in Table II. At any concentration of acid over 0·1N., they lead to appreciably different results, and these differences would be particularly important in any attempt to study the dissociation equilibrium of the resin quantitatively. For such a purpose it would be necessary to know the small number of basic groups, per g. of resin, still un-ionised at high concentrations of acid; but with no criterion to guide us as to the correct equation to use, any calculated figure would be totally unreliable. It will be noticed also that all four equations used in Table II show a feature that is almost certainly artificial, a maximum in the acid adsorption curve. This, and much independent evidence on the swelling of resins, leads us to conclude that equilibrium studies of acid adsorption are quite unreliable unless accompanied by simultaneous measurements of the adsorption of water by the resin. Similar criticisms and conclusions apply to dissociation studies of weak acid resins at high pH values and high salt concentrations.

Before leaving equations (5) and (6), we derive the relation between Γ_{HCl} and Γ^1_{HCl}, as this will be useful later. We have

$$\Gamma_{HCl} - \Gamma^1_{HCl} = \frac{1}{r}\left[\frac{mv(d - nM/1000) + mw}{(d' - mM/1000)} - mv'\right]$$

$$= \frac{m}{r}\left[\frac{v(d - nM/1000) + w - v'(d' - mM/1000)}{(d' - mM/10000)}\right]$$

$$= m\Gamma^e_{H_2O}/(d' - mM/1000) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

That is, the correction to be added to Γ^1_{HCl} to obtain the true adsorption of HCl is:

$$\Gamma^e_{H_2O} \frac{\text{milliequivs. of HCl in 1 g. of equilibrium solution}}{\text{g. of } H_2O \text{ in 1 g. of equilibrium solution}}$$

Water-adsorption Measurements.—To determine both water and acid adsorption at least two analyses are necessary, and in addition some assumption must be made as to the distribution in the system of a third reference substance. The experiments reported in Tables III and IV were designed to this end. Weighed samples of resin were equilibrated with hydrochloric acid solutions containing added chlorides. All analyses were based on weights, and the solutions before and after contact were analysed for both acid and total chloride. It was assumed, in the first place, that the added salt was not adsorbed by the resin. This enabled the system to be arbitrarily divided into two phases:

(*A*.)	(*B*.)
Solution, containing H_2O, HCl, and XCl.	Resin + adsorbed H_2O + adsorbed HCl.

This provides self-consistent values for the adsorbed water and acid, but does not preclude the subsequent adjustment of the model to include part of phase *A* (*i.e.*, the three constituents in their known proportions) in the resin phase if independent evidence for the presence of salt in the resin can be adduced. The adsorptions were calculated as follows: Let the initial system consist of r g. of dry resin + w g. of water; s g. of XCl, h g. of HCl, and W g. of H_2O. After contact, the weight, a g. of the solution containing s g. of XCl is calculated; the weight, b g. of HCl in a g. of solution is then found, hence the composition of the solution is s g. of XCl, b g. of HCl, and $(a - s - b)$ g. of H_2O; and therefore:

$$\Gamma^e_{H_2O} = [W + w - (a - s - b)]/r \text{ g. per g. of dry resin}$$

and

$$\Gamma_{HCl} = \frac{1000}{36{\cdot}47}\frac{(h - b)}{r} \text{ milliequivs. per g. of dry resin} \quad . \quad . \quad . \quad . \quad (8)$$

The data are tabulated in this way in Tables VI and VII.

TABLE VI.

Equilibrium acid concn. approx. 0·04N. $r = 1{\cdot}012$ grams.

Nos.	s.	h.	$W + w$.	a.	b.	$a - s - b$.	Γ_{HCl}.	$\Gamma^e_{H_2O}$.
3, 4	0·29411	0·47083	99·50	98·56	0·15294	98·11	8·615	1·37
5, 6	1·1682	0·47078	99·30	99·29	0·14617	97·98	8·796	1·31
7, 8	5·8327	0·47561	97·82	102·95	0·13942	96·98	9·111	0·83
9, 10	11·656	0·48006	95·83	106·97	0·13415	95·18	9·374	0·64
11, 12	23·168	0·48438	91·45	114·28	0·12598	90·99	9·713	0·45

In Curve 1 of Fig. 1 the water adsorptions at both acid concentrations are plotted against the total chloride concentration of the solution (given in Tables III and IV). Except for the determination in barium chloride the points for both series lie very close to a common curve.

TABLE VII.

Equilibrium acid concn. approx. 0·1N. $r = 1{\cdot}012$ grams.

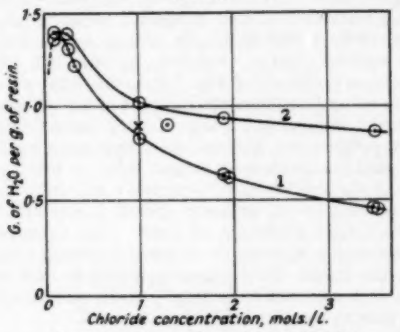
Nos.	s.	h.	$W + w$.	a.	b.	$a - s - b$.	Γ_{HCl}.	$\Gamma^e_{H_2O}$.
15, 16	1·1637	0·74876	99·15	99·49	0·41177	97·91	9·133	1·22
17, 18	11·541	0·75008	95·67	106·98	0·39361	95·05	9·661	0·62
19, 20	23·070	0·74733	91·28	114·27	0·37985	90·82	9·959	0·45
21, 22 *	13·830	0·74938	97·51	110·82	0·39789	96·59	9·526	0·90

* Added salt: barium chloride.

At first sight this appears surprising, since the acid adsorption, and therefore the ionisation of the resin, is appreciably greater in the second series, and it might be thought that this would lead to greater swelling and higher Γ_{H_2O} values. The whole picture, however, closely resembles the Donnan effects for weak electrolyte colloids, such as gelatin (Loeb, *J. Gen. Physiol.*, 1918, **1**, 363). At very low acid concentrations the ionisation of the resin, and therefore the swelling pressure, will be increasing very rapidly with increasing concentration; but, as Table II shows, the resin is already highly ionised in 0·02N-acid, and thereafter the increasing ionic concentrations in the outer solution become the dominant factor, and the counter-osmotic pressure leads to a maximum followed by the curve of Fig. 1. Some evidence for this view is provided by the point for the barium chloride solution. If we correct for the bivalent cation (assuming ideal-solution laws) by plotting number of ions in outer solution instead of chloride concentration, we obtain the point marked by a cross, which agrees as closely as would be expected with the curve for sodium chloride additions.

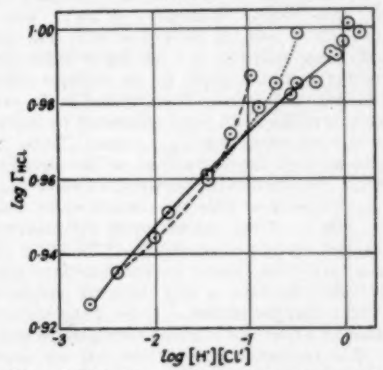
If this explanation of the curve in Fig. 1 is qualitatively correct, then at all acid concentrations above 0·04N. the water adsorption will be determined almost entirely by the total

FIG. 1.



Curve 1: Γ_{H_2O}; *Curve* 2: *total* H_2O *per g. of resin.*

FIG. 2.



Plot of Bishop's equation. Data from Table VI ———; from Table VII . . . .

concentration of the ambient solution, and will be insensitive to the actual acid concentration. For evaluating the small correction term given in equation (7) we have therefore read Γ_{H_2O} values from Fig. 1, Curve 1. Application of this procedure to the salt-free points of Tables III and IV and to the experiments of Table V provides the further Γ_{HCl} figures reported in Col. 5 of Table VIII.

TABLE VIII.

	Equilibrium concns.:					Equilibrium concns.:			
No.	acid.	chloride.	Γ_{H_2O}.	Γ_{HCl}.	No.	acid.	chloride.	Γ_{H_2O}.	Γ_{HCl}.
1, 2	0·04442	0·04444	1·40	8·45	28	0·9211	0·9211	0·86	9·83
13, 14	0·1175	0·1175	1·37	8·93	29	0·9070	1·103	0·80	9·91
23	0·5243	0·5243	1·08	9·60	30	0·8421	1·794	0·64	9·97
24	0·5224	0·621	1·02	9·66					
25	0·5118	0·999	0·83	9·67	31	1·794	1·794	0·64	9·94
26	0·5059	1·461	0·70	9·85	32	1·776	1·969	0·62	10·03
27	0·4844	2·331	0·57	10·02	33	1·725	2·662	0·53	10·00

The adsorption figures so far presented are based on the convention that the adsorption of salt is zero. There is no reason to suppose that salt is entirely excluded from the resin phase, and there is some evidence to the contrary (cf. Bauman and Eichhorn, *J. Amer. Chem. Soc.*, 1947, **69**, 2831).

The Donnan theory may again be invoked here to provide a rather more accurate picture of actual conditions in the resin. For instance, in Expts. 3 and 4 of Table VI, the system has so far been arbitrarily divided into homogeneous solution consisting of 98·11 g. of water, 0·2941 g. of NaCl (0·05105 weight normal) and 0·1529 g. of HCl (0·04255 weight normal); and a resin

phase containing the surface excess of acid and water, the proportions being: 1 g. of resin, 1·37 g. of water, and 8·615 milliequivs. of acid. The arbitrary boundary between the phases may now be moved, as it were, further from the resin surface, so that part of the solution constituents are included in the resin phase; and the true position is fixed by the Donnan equation of products:

$$[a_{Na^+}.a_{Cl'}]_{Resin} = [a_{Na^+}.a_{Cl'}]_{Solution}$$

Here we encounter the well-known difficulties that the ion activities in the resin phase are not known, and that the resin hydrochloride may not be completely dissociated. However, an approximate solution is enlightening, and if we replace activities by weight-concentrations, and assume complete dissociation, we have:

$$\frac{0{\cdot}051x(8{\cdot}615 + 0{\cdot}0936x)}{(x + 1{\cdot}37 + 0{\cdot}3142)^2} = 0{\cdot}05105 \times 0{\cdot}0936$$

where x is the number of g. of solution included per g. of dry resin. The equation gives $x = 0{\cdot}0327$ g., and although the percentage error in this figure may be high, its order of magnitude will be correct. It leads to the following composition of the resin phase: 1 g. of resin (8·617 milliequivs. protonated), 1·40 g. of H_2O, 8·617 milliequivs. of Cl', 0·0014 milliequiv. of H^+, and 0·00167 milliequiv. of Na^+. The weight-normal concentrations in the resin phase are: $Cl' = 5{\cdot}01$, $H^+ = 8{\cdot}07 \times 10^{-4}$, and the approximate potential difference between resin and outer solution is: $58 \log [0{\cdot}04255/(8{\cdot}07 \times 10^{-4})] = 100$ millivolts, which agrees with another estimate made by an entirely different method (Davies, *Biochem. J.*, **1949**, **45**, 38). The other points have been treated in the same way, and Curve 2 of Fig. 1 gives the total water content of the resin per g., obtained by adding the water just introduced as part of the solution to the corresponding Γ_{H_2O} value. These calculated values may carry a very considerable error at high concentrations, as has already been pointed out, and the most important result of the calculations is, perhaps, to show that at acid concentrations around 0·1N. or less, the Γ_{H_2O} values must give the correct water content of the swollen resin to within a few units %; *i.e.*, 100 g. of the ionised resin comprising approximately six or seven carbon atoms and a nitrogen atom, are accompanied by 140 g., or about eight molecules, of water. The extended resin, therefore, seems to accommodate approximately a monolayer of water containing the chloride gegen-ion, a very different picture from the diffuse double layer supposed to exist at a plane charged surface. Even if the hydrochloride is assumed to be largely undissociated the value of x does not increase very greatly and the picture remains sensibly unchanged.

The Ionisation Equilibrium.—If our object were to estimate the total acid present in the resin, treating this as a homogeneous phase, then the values for hydrogen chloride in Tables VI, VII, and VIII, like those for the water adsorption, would be subject to a small correction for the free hydrogen and chloride ions necessary to satisfy the Donnan equation of products. The uncorrected figures are of more interest, however, as these clearly measure the amount of hydrogen ion bound by the resin, that is, the extent of ionisation.

Bishop (*loc. cit.*) has studied the adsorption of a number of acids by basic resins, and has reported an approximately linear relationship between the logarithms of the amount of acid adsorbed and of the concentration product of hydrogen ion and anion in the equilibrium solution. This is not obeyed by our data, as will be seen from Fig. 2, where the values of Tables VI—VIII are plotted in this way. The points lie reasonably close to a common line so long as the concentration of neutral chloride is not high, but there are regular deviations at the higher concentrations.

Bauman ("Ion Exchange," ed. F. C. Nachod, Academic Press, N.Y., 1949, p. 68) has outlined an approximate treatment of the ionisation equilibrium of a weak basic resin which can be applied to our results as follows. For the process $R{\cdot}NH_3{\cdot}OH + H^+ + Cl' \rightleftharpoons R{\cdot}NH_3^+ + Cl_s' + H_2O$ the (concentration) equilibrium constant is written:

$$K = [R{\cdot}NH_3^+][Cl']_R/[R{\cdot}NH_3{\cdot}OH][H^+]_S[Cl']_S$$

where the suffixes R and S refer to resin phase and solution phase, respectively. If we eliminate $[Cl']_R$ from this equation by means of the Donnan relation $[Cl']_R/[OH']_R = [Cl']_S/[OH']_S$, and multiply by $K_w = [H^+][OH']$, we obtain

$$KK_w = [R{\cdot}NH_3^+][OH']_R/[R{\cdot}NH_3{\cdot}OH] = K_B$$

where K_B is the basic dissociation constant of the resin. K can be evaluated from the experimental data if we put $[Cl']_R = \Gamma_{HCl}$, and

$$[R{\cdot}NH_3^+]/[R{\cdot}NH_3{\cdot}OH] = \Gamma_{HCl}/(C - \Gamma_{HCl})$$

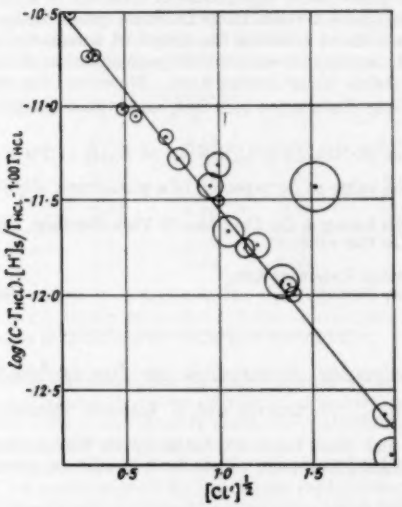
where C is the total combining capacity, in milliequivs. per g. of the resin. Values of K_R derived in this way for the salt-free solutions are given in Table IX. The value of C is fixed within fairly close limits, on the one hand by the adsorption of slightly over 10 milliequivs. per g. at the highest concentrations, and on the other by the nitrogen content of the resin, which corresponded for Batch B with a theoretical capacity of approximately 10·3 milliequivs. We used the value $C = 10{\cdot}10$, but the conclusions reached would not be invalidated by any reasonable change in the value taken.

TABLE IX.

Nos.	$[H^+] = [Cl']$.	Γ_{HCl}.	log K_R.	Nos.	$[H^+] = [Cl']$.	Γ_{HCl}.	log K_R.
1, 2	0·04440	8·45	$\overline{1}0{\cdot}342$	28	0·9211	9·83	$\overline{1}2{\cdot}625$
13, 14	0·1175	8·93	$\overline{1}1{\cdot}673$	31	1·794	9·94	$\overline{1}2{\cdot}283$
23	0·5243	9·60	$\overline{1}2{\cdot}827$				

This treatment involves several approximations. Concentrations, and not activities, have been used throughout; it is assumed that all the basic groups of the resin are equivalent in position and inherent strength; the resin hydrochloride is assumed to be completely dis-

FIG. 3.



sociated, and changes in swelling and swelling pressure are ignored (the concentration unit of K_R is moles/kg. of dry resin). Clearly, one or more of these assumptions must be completely at variance with the facts. Not only does K_R vary by more than 100-fold for a comparatively narrow range of Γ_{HCl} values, but the magnitude of K is many powers of ten smaller than would be expected for the basic constant of aliphatic amino-groups.

An approach to the problem involving fewer explicit assumptions can be made in the way proposed by Hartley and Roe (*Trans. Faraday Soc.*, 1940, **36**, 101) for a somewhat similar problem.

If all the ionising groups in the resin are equivalent, the primary ionisation process should conform to the equilibrium condition

$$K = [R{\cdot}NH_2][H^+]^*/[R{\cdot}NH_3^+] = (C - \Gamma_{HCl})[H^+]^*/\Gamma_{HCl}$$

where the term $[H^+]^*$ is the concentration of hydrogen ion at the resin surface, and represents the probability of a hydrogen ion arriving at the critical distance from a $R{\cdot}NH_2$ site for ionisation to occur. $[H^+]^*$ will be related to the concentration of hydrogen ion in the equilibrium solution by the equation

$$[H^+]^* = [H^+]_s e^{-W/RT}$$

where W is the work done in transporting a hydrogen ion from the solution to the resin surface, partly against electrical forces and partly against the forces opposing swelling. In our experiments the concentrations of acid and added salt were both varied, and as the two independent variables in analysing the data we take Γ_{HCl} and $[Cl']$. The former is primarily responsible for the density of the positive charge carried by the resin, and for the degree of swelling; the latter, the total ionic concentration, influences both the potential difference between the resin and the solution phase, and the counter-osmotic pressure. By interpolating from our data, the effects of the two terms were considered separately, and in this way we were led to the equation

$$\log K = \overline{1}\cdot71 = \log (C - \Gamma_{HCl})[H^+]_s/\Gamma_{HCl} - 1\cdot00\Gamma_{HCl} + 1\cdot24[Cl']^{\frac{1}{2}} \quad . \quad . \quad (9)$$

That the data should depend on the square-root of the total concentration was unexpected, and this dependence is probably not exact, but it will be seen from Fig. 3 that the equation expresses the results within the experimental uncertainty.

The size of the circles drawn round the points indicates the effect of a 0·2% error in the adsorption measurements. The three measurements numbered 31—33 are omitted from Figs. 2 and 3 as this series shows irregularity; we think that the resin structure is not stable at such high acid concentrations and that swelling in these cases was greater than was assumed in the calculations. No quantitative significance is attached to equation (9), as the constants (representing the opposing effects of resin charge and ionic concentration) could be simultaneously modified by 5% or more without affecting the extent of agreement with the data. The wide variations in acid and salt concentrations covered by an equation of this form suggest, however, that the approach is probably along correct lines. Moreover, the mean value of log K, *viz.*, $\overline{1}\cdot71$, corresponds to a basic dissociation constant, under ideal conditions of zero ionic strength and zero charge, of

$$K_B = [R\cdot NH_3^+][OH']/[R\cdot NH_2] = K_w/K = 2\cdot0 \times 10^{-4}$$

which agrees well with the value to be expected of a monomeric aliphatic amine.

We thank Messrs. Charles Lennig & Co. Ltd., 18—20 York Buildings, London, W.C.2, for supplying the Amberlite IR-4B used in this work.

EDWARD DAVIES CHEMICAL LABORATORIES,
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583. *Molecular Adsorption on Ion-exchange Resins.*

By C. W. DAVIES and G. GARROD THOMAS.

Weak acids and weak bases are taken up by ion-exchange resins by a process of molecular adsorption. Data for a number of systems are reported and discussed.

BRIEF references to this work have already been made (Davies, *Chem. and Ind.*, 1948, 51; 1949, 25), and the importance of adsorptive forces in ion-exchange chromatography has been emphasised (*idem, Biochem. J.*, 1949, **45**, 38). A short record of our measurements will therefore be sufficient.

EXPERIMENTAL.

Materials.—The resins used were four cation exchangers in the hydrogen form: Wofatit C, which contains only carboxylic acids groups; and Zeo-Karb 215, Amberlite IR-100, and Zeo-Karb H1, which are strong acid exchangers, but contain phenolic and carboxylic as well as sulphonic acid groups. The Zeo-Karb 215 was dry sieved to three sizes, 20/40 mesh, 60/90 mesh, and a fine sample passing 100 mesh. The Wofatit and Amberlite were sieved to 20/40 mesh, and the Zeo-Karb H1 was used as received. The resins were conditioned in the usual way, and were air-dried after prolonged washing with distilled water. At the time each series of adsorption measurements was begun, the moisture content of the resin was determined by heating separate samples to constant weight.

Adsorption of Organic Acids.—Some measurements to study the effect of particle size were carried out with the Zeo-Karb 215, but Wofatit C and Amberlite IR-100 were used for the bulk of the work. The organic acids were the purest laboratory reagents available, and were used without further purification. 2-G. samples of resin were weighed into bottles with tightly fitting ground stoppers. 50 Ml. of a standard acid solution were added to each from a calibrated pipette, and the bottles were kept at room temperature with daily agitation for 28 or 56 days; in the rate experiments the time of

contact was varied. Two 20-ml. aliquots were then withdrawn and titrated against standard baryta with phenolphthalein as indicator. Each series was accompanied by blank experiments (2 g. of resin; 50 ml. of water) and in the adsorption calculations it was assumed that the resin lost acid to the solutions studied at the same rate as to water.

There are two main sources of error in the results. First, no allowance has been made for swelling. Water is simultaneously adsorbed, with the result that our calculated apparent adsorption of acid will be too low. From the available information on commercial resins we estimate that approximately $N/2$ milliequivs. per g. should be added to our adsorption figures, where N is the equilibrium acid normality. This is supported by some measurements with 0·1N-hydrochloric and sulphuric acids, which showed an apparent *negative* adsorption of acid of approximately 0·05 milliequiv. per g. The second uncertainty is in the blank correction. Many investigators have found that these resins in the hydrogen form are not entirely stable, and our blank corrections were often quite considerable. If, now, acid diffuses less readily from the resin into the acid solutions than into water, our calculated adsorptions, especially in the more concentrated solutions of low pH, will be too high. It is unknown how important this effect is, but it will act in opposition to the other source of error, and by neglecting both we think that our results will only exceptionally be in error by more than 1 or 2 units %.

Adsorption of Bases.—The adsorption of ammonia and pyridine was studied on Zeo-Karb H1 and Amberlite 1R-100. Bromocresol-purple and bromophenol-blue, respectively, were used as indicators in the final titration against standard acid. 1-G. samples of resin and 100 ml. of solution were used in this work, so swelling errors were less important. Blank experiments were carried out as before.

Results and Discussion.

The adsorption of organic acids on Wofatit C can be adequately represented by the Freundlich equation, as Fig. 1 shows, and the same is true of Amberlite 1R-100. This provides a convenient basis for tabulation, and our results for these two resins are as follows :

	Wofatit C.			Amberlite 1R-100.		
Acid.	A	n	$(x/m)_{0\cdot01}$	A	n	$(x/m)_{0\cdot01}$
Phenylacetic	8·3	1·43	0·331	9·0	1·55	0·466
Benzoic	15·2	1·38	(0·536)	35	1·2	(0·73)
Phthalic	6·9	1·28	0·192	—	—	—
Octanoic	—	—	—	18·1	1·39	(0·63)
Butyric	3·06	1·18	0·063	2·96	1·35	0·098
Acetic	1·48	0·97	0·013	1·31	1·09	0·019
Adipic	7·6	1·09	(0·11)	—	—	—
Glutaric	3·2	1·10	0·051	—	—	—

Cols. 2 and 3 show the values of A and n in the equation $x/m = AC^{1/n}$, where x/m is the adsorption in milliequivs. per g. of dry resin, and C is the concentration of acid at equilibrium. Col. 4 shows the adsorption in milliequivs. from a 0·01N-solution, the figures in parentheses being extrapolated values.

If the effect is one of molecular adsorption on the resin framework, the nature of the ionising groups of the resin would not be expected to be of overriding importance, and actually it will be seen that the adsorption of acids is considerably *greater* on the strong sulphonic acid Amberlite resin than on the carboxylic acid Wofatit resin.

Some measurements on both resins in the presence of added hydrochloric acid are compatible with the view that it is the undissociated acid molecule that is adsorbed. The effect of the hydrochloric acid in every case was to increase the adsorption by an amount commensurate with the slight increase in the concentration of undissociated acid at equilibrium.

The measurements on Zeo-Karb 215 were not over a wide enough concentration range to provide values of A and n, but at the concentrations studied the adsorptions of phenylacetic, phthalic, butyric, and acetic acids were almost the same as on Wofatit C. That for mandelic acid came between the figures for butyric and phthalic, and, as would be expected, formic acid was less adsorbed than acetic, and succinic less than glutaric acid.

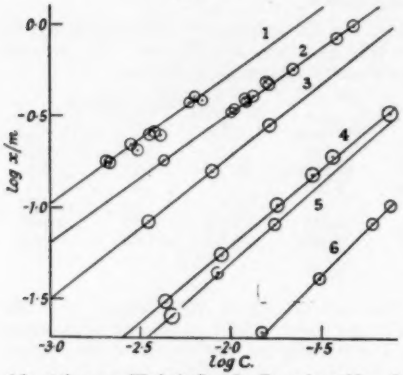
The value of n is close to 1 for acetic and the other weakly adsorbed acids. The equilibrium in these cases might be described as a simple distribution of solute between the resin phase and the outer solution. It has been shown before, however (preceding paper), that the amount of water taken up by a typical commercial resin from aqueous solution is only sufficient to provide an approximately unimolecular film of water on the internal surface of the resin, so the analogy with typical cases of surface adsorption seems more likely to be useful. For the more highly adsorbed acids n is greater than 1, but at the concentrations studied there is no evidence of curvature in the Freundlich plots. The highest adsorption measured was 1·19 milliequivs. per g. of Amberlite resin for phenylacetic acid at an equilibrium concentration of 0·0426N. If the extended resin framework is assumed to present its whole surface to the intermicellar liquid, this would correspond to 6 or 7% of the surface being covered by acid

molecules. This, and the fact that the Freundlich plot shows no sign of a saturation limit, suggests that at higher concentrations the adsorption of an aromatic acid might reach values as great as or even greater than the maximum ion-exchange capacity of the resin.

The order of adsorbability of the various acids studied is the same on all three resins as on an active carbon. The aromatic acids are strongly adsorbed. Traube's rule is obeyed by both the monocarboxylic and the dicarboxylic series of aliphatic acids, and the effect of polar substituents, as in phthalic and mandelic acids, is to reduce adsorption from aqueous solutions. Other examples of this, not previously mentioned, are citric and tartaric acids, which we found to be only very weakly adsorbed on Zeo-Karb 215.

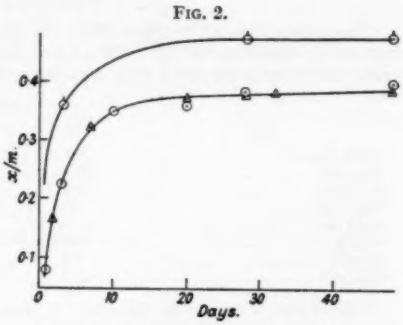
Effect of Particle Size.—Measurements with most of the acids so far mentioned were carried out on the three graded samples of Zeo-Karb 215, and the amount adsorbed was found to be independent of particle size. There did appear to be an effect, however, with benzene-, naphthalene-2- and anthraquinone-sulphonic acids. These three strong acids showed negligible adsorption on the larger resin granules but appreciable adsorption on the sample passing 100-mesh. The size of this effect is rendered a little uncertain by the large " blank " correction given by the fine resin, but it seems worthy of further study. It seems to suggest that these

FIG. 1.



Adsorption on Wofatit C : 1, *Benzoic acid ;* 2, *phenylacetic acid ;* 3, *phthalic acid ;* 4, *butyric acid ;* 5, *glutaric acid ;* 6, *acetic acid.*

FIG. 2.



○ *Phenylacetic acid on Wofatit C ;*
○ *phenylacetic acid on Amberlite* IR-100 *;*
△ *benzoic acid on Wofatit C.*

anions are unable to diffuse into the resin interior, but are heavily adsorbed at the external surface.

Adsorption of Bases.—When aqueous pyridine solutions were equilibrated with Zeo-Karb H1 there was a loss of pyridine from the solution of 2·1 milliequivs. per g. at low residual concentrations of pyridine, corresponding to salt formation at the sulphonic acid groups. At higher concentrations the amount of pyridine removed from the solution increased progressively to 5·9 milliequivs. at 0·57N. This increase is far greater than can be explained by the ionisation of the carboxylic groups contained in Zeo-Karb H1 (cf. Davies, *Chem. and Ind.*, 1948, 52), and salt formation between the phenolic groups and so weak a base as pyridine will be scarcely appreciable. Almost the whole of the additional 3·8 milliequivs. of pyridine removed by the resin must therefore be regarded as held by molecular adsorption.

In similar experiments with aqueous ammonia solutions, the amount of ammonia held by Amberlite 1R-100 increased to 4·31 milliequivs. at an equilibrium concentration of 0·270N. This is considerably greater than the amount of sodium hydroxide neutralised at the same pH, so here too there is some evidence for the adsorption of ammonia molecules, though, as would be expected, the effect in this case is much less marked.

Rate of Adsorption.—Fig. 2 shows some measured rates of adsorption for benzoic and phenylacetic acids. The slowness of the reverse process, also, was shown in some experiments in which resin was added to 0·06N-phenylacetic acid, and left in contact for 18 days, an equal quantity of water then being added. After a further 32 days the adsorption, on both Wofatit C and Amberlite 1R-100, was significantly greater than in experiments where the additional water

had been present from the beginning of the 50-day period. The tenacity with which pyridine is held by Zeo-Karb H1, Amberlite 1R-100, and Wofatit C was shown in a series of experiments in which samples of the resin, after being treated overnight with 0·5N-pyridine solutions, were washed with water and successive portions of hydrochloric acid (1 g.-mole per g. of resin in all), over a period of months. After this treatment the resins gave the characteristic odour of pyridine when treated with sodium hydroxide.

With simpler and less heavily adsorbed molecules the rates of adsorption and desorption are probably much greater than in the above cases. No further adsorption of butyric acid could be detected after 6 days' contact.

We thank the Department of Scientific and Industrial Research for the award of a maintenance allowance, during the tenure of which (by G. G. T.) this work was carried out.

EDWARD DAVIES CHEMICAL LABORATORIES, ABERYSTWYTH. [*Received, April 30th*, 1951.]

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584. *Reactions of Hypochlorous Acid and Sodium Hypochlorite at the Dropping Mercury Electrode.*

By E. N. JENKINS.

A set of double polarographic waves have been obtained, by use of the dropping mercury electrode, for 10^{-4}M-hypochlorous acid on step-wise neutralisation with sodium hydroxide. The waves are shown to represent the products of simple chemical reactions at the mercury surface.

AN earlier study of the polarography of hypochlorites in which the dropping mercury electrode was used (Heller and E. N. Jenkins, *Nature*, 1946, **158**, 706) was mainly concerned with the analysis of commercial sodium hypochlorite solutions, containing sodium chloride and dissolved oxygen, in the presence of chloramines. It was concluded that the hypochlorite ion is "one of the oxygen-containing anions which are irreversibly reducible at the dropping mercury electrode" with a half-wave potential +0·08 v. (saturated calomel electrode) in neutral 0·5N-potassium sulphate at room temperature. Further investigations by Heller and I. L. Jenkins (Jenkins, Thesis, Univ. of Wales, 1950) showed that acidified solutions of fairly chloride-free sodium hypochlorite gave double polarographic waves; these investigations were curtailed by the death of Dr. K. Heller while the results were yet inconclusive. The present work was aimed at obtaining reproducible polarograms of pure hypochlorous acid and sodium hypochlorite, at concentrations around 10^{-4}M. (where the curves are free from maxima) and in the presence of 0·1M-potassium nitrate, in order to establish the nature of the electrode processes.

EXPERIMENTAL.

Reagents.—Solutions of hypochlorous acid (about 0·1M.) were prepared in Pyrex apparatus, under the minimum of illumination, by chlorination of a suspension of yellow mercuric oxide, followed by distillation under water-pump vacuum. Chemical analysis of the solutions revealed no significant amounts of mercury salts, hydrochloric acid, or chlorous acid; the remaining oxy-acids of chlorine and their salts are not reducible at the dropping mercury electrode (Rylich, *Coll. Czech. Chem. Comm.*, 1935, **7**, 288). The solutions were relatively stable at room temperature if protected from light, losing as little as 1·5% of their initial strength in 4 weeks.

The potassium nitrate was a recrystallised analytical-grade specimen. All solutions were made up in conductivity water, prepared by the mixed-bed de-ionisation method (Davies and Nancollas, *Chem. and Ind.*, 1950, **7**, 129). The sodium hydroxide solution was carbonate-free.

Apparatus.—The manual polaroscope used consisted of a calibrated potentiometer wire, sensitive damped galvanometer, and Ayrton shunt. The Pyrex electrolysis cell, maintained at 25·0°, was fitted with a detachable, non-polarisable mercury–mercurous sulphate–saturated potassium sulphate half-cell of potential $+0{\cdot}390 \pm 0{\cdot}002$ v (against a saturated calomel electrode at 25°, with an intermediate solution of 0·1M-potassium nitrate. All potentials quoted hereafter are referred to the saturated calomel electrode). Electrical contact with the solution in the main cell was made around the periphery of an ungreased tap. The resistance thus introduced, about 20,000 ohms, was measured frequently and the potentials corrected for the *IR* drop across the cell. The dropping mercury electrode had the characteristics: $m = 1{\cdot}68$ mg. sec.$^{-1}$ (fixed head of mercury); $t = 4{\cdot}2$ sec. (−0·5 v, 0·1M-potassium nitrate).

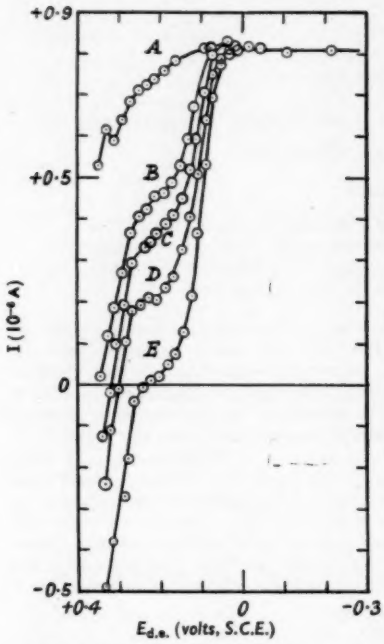
Method.—Solutions were made up by weight, stock hypochlorous acid being added to the cell from a weight burette, with mechanical stirring and exclusion of oxygen. Mercury was not allowed to accumulate in the cell before start of the electrolysis, and the experiments were made under the

minimum of illumination. The mean values of the galvanometer oscillations were recorded. The bulk concentration of hypochlorite was reduced only very slowly by the mercury, as was demonstrated by amperometric and chemical analyses. The polarograms were corrected for the residual currents, previously determined.

Results and Discussion.

The cathodic double wave obtained for 10^{-4}M-hypochlorous acid in 0·1M-potassium nitrate of pH 5·5 (Fig. 1, curve *B*) was perfectly reproducible. The results lose significance at potentials more positive than about +0·35 v, owing to interference from the anodic dissolution wave of mercury. The overall limiting currents were measured at −0·50 v, in solutions of strengths $2{\cdot}5 \times 10^{-5}$ to $3{\cdot}7 \times 10^{-4}$M., with and without added sodium hydroxide. In each "run," four or five successive additions of stock hypochlorous acid were made to the cell solution. While the ratio I_d/C remained constant within ±2% or better in a given "run," variations of up to 10% appear between the mean values of different "runs." These variations could not be correlated with the amount of added alkali, and may be caused by variations in the low "chlorine demand" of the freshly prepared supporting electrolyte solutions. Within the above limits, the ratio I_d/C is the same for undissociated hypochlorous acid as for the hypochlorite ion; their respective diffusion coefficients must then agree to within 20%. The specific conductivity of 1×10^{-3}M-sodium hypochlorite at 25° is $1{\cdot}15 \times 10^{-4}$ reciprocal ohms (Noyes and Wilson, *J. Amer. Chem. Soc.*, 1922, **44**, 1630), thus the equivalent ionic conductance of the hypochlorite ion is about 65 (on the assumption that $\Lambda^{25}_{Na^+} = 50$). By use of the equation $D = 2{\cdot}67 \times 10^{-7}\Lambda$, the diffusion coefficient of the hypochlorite ion may be calculated approximately as $1{\cdot}7 \times 10^{-5}$ cm.^{2} sec.$^{-1}$. The highest mean value of I_d/C for hypochlorite solutions containing excess of alkali was 8·5 μA l. millimol.$^{-1}$. Application of the Ilkovic equation, $n = I_d/605Cm^{\frac{2}{3}}t^{\frac{1}{6}}D^{\frac{1}{2}}$, yields $n = 1{\cdot}9$. If the correct value is assumed to be 2 electrons consumed per electrode process involving one hypochlorite ion, the diffusion coefficient may be recalculated as $1{\cdot}5 \times 10^{-5}$ cm.^{2} sec.$^{-1}$ (0·5M-potassium nitrate, 25°).

Fig. 1.



The polarograms obtained for a series of approx. 10^{-4}M-hypochlorous acid solutions containing added acid or alkali (Fig. 1; Table) are free from maxima. The values of the electrolysis currents have been adjusted by an appropriate factor, where necessary, to bring the diffusion currents at 0·0 v. in each case to 0·81 μA (the mean value of I_d/C for this series being 8·1). The recorded pH values (glass electrode) are only approximate.

Half-wave potentials and currents for hypochlorite double waves.

[NaOH]/[HOCl] or [HNO_2]/[HOCl]	pH	Curve	$E'_{\frac{1}{2}}$ (v)	$E''_{\frac{1}{2}}$ (v)	I' (μA)	I'' (μA)
1·07 (HNO_2)	4·4	*A*	—	—	—	—
0·00	5·5	*B*	+0·298	+0·122	0·46	0·35
0·20 (NaOH)	6·2	*C*	+0·303	+0·109	0·545	0·44
0·365 ,,	6·7	—	+0·288	+0·084	0·36	0·54
0·60 ,,	7·5	*D*	+0·308	+0·107	0·525	0·605
0·775 ,,	9·0	—	+0·294	+0·102	0·57	0·675
1·00 ,,	9·8	*E*	+0·297	+0·099	0·58	0·79

In the Table, $E'_{\frac{1}{2}}$ and I' are the half-wave potential and height respectively of the initial cathodic, anodic, or composite anodic-cathodic wave (+0·35 to +0·20 v); $E''_{\frac{1}{2}}$ and I'' refer to the subsequent cathodic wave. From Fig. 2, the ratio I''/I_d is seen to increase linearly with the

ratio $[NaOH]_{added}/[HOCl]_{added}$, rather than with any of the equilibrium ratios $[OCl^-]/([OCl^-] + [HOCl])$, calculated for a dissociation constant, K_{HOCl}, in the range 10^{-7}—10^{-8}. (Various values for K_{HOCl} appear in the literature; recent determinations at 25° are largely within the above range.) Curves *B*—*E* of Fig. 1 form a series of double waves of approximately constant half-wave potentials (+0·30 and +0·10 v respectively). Whereas the magnitude of the first wave remains roughly constant, the second wave increases linearly with the amount of added alkali, from about half the overall cathodic limiting current (hypochlorous acid) to almost the entire limiting current (sodium hypochlorite). These results may be interpreted in terms of an immediate chemical reaction of hypochlorous acid and sodium hypochlorite respectively at the mercury surface (Wolters, *J. pr. Chem.*, 1873, **7**, 468; 1874, **10**, 128):

(i) $2HOCl + 2Hg = (HgO + HgCl_2) + H_2O$.

Under the conditions of the present experiments, the compounds in parentheses do not appear to exist as an oxychloride Hg_2OCl_2, and the mercuric chloride is immediately and almost

FIG. 2.

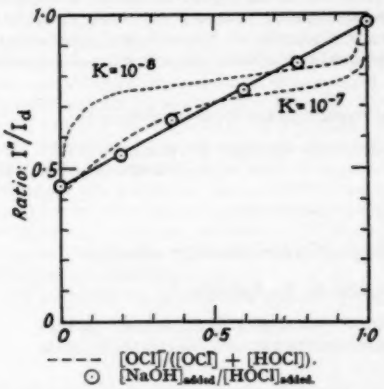
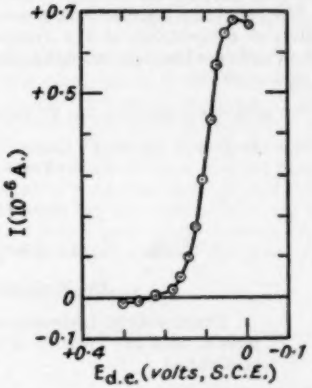


FIG. 3.



completely converted into calomel (Kolthoff and Miller, *J. Amer. Chem. Soc.*, 1941, **63**, 2732):

(ii) NaOCl (or NaOH + HOCl in hydrolysis equilibrium) + Hg = HgO + NaCl (+H_2O).

The first of the hypochlorite double waves is then caused by the reversible cathodic reduction of calomel, the reversible anodic depolarisation of mercury by chloride ion, or by mixed anodic-cathodic processes. Since the total chloride content as (chloride ion plus combined chlorine in calomel) remains constant throughout the series, the height, half-wave potential, and equation of the wave do not change. Kolthoff and Miller report a value of +0·25 v, both for the half-wave potential of 10^{-3}M-chloride (*J. Amer. Chem. Soc.*, 1941, **63**, 1405) and for the half-wave potential of $0·5 \times 10^{-3}$M-mercuric chloride (*ibid.*, p. 2732). A ten-fold decrease in these concentrations should displace the half-wave potential by +0·06, *i.e.*, to +0·31 v (Found, see table: +0·29 to +0·31 v).

The second wave is caused by the reversible cathodic reduction of dissolved mercuric hydroxide (saturated solution = $2·4 \times 10^{-4}$M. in water at 25°):

$$Hg(OH)_2 + 2e \longrightarrow Hg + 2OH^-$$

The theoretical equation of the reduction wave of weakly dissociated mercuric hydroxide in the absence of excess of hydroxide ion (cf. the similar case of mercuric cyanide, Kolthoff and Lingane, "Polarography," Interscience Publ., New York, 1946, p. 181) is:

$$E_{d.e.} = E' - 0·0296\log_{10} I^2/(I_d - I)$$

Under the above conditions, the equation and half-wave potential depend only on the initial concentration of mercuric hydroxide at the electrode surface, and are independent (*e.g.*, in the case of partly neutralised hypochlorous acid solutions) of the pH value in the bulk solution.

Fig. 3 is the polarogram obtained with oxygen-free 0·1M-potassium nitrate, half saturated with yellow mercuric oxide at room temperature ($\simeq 10^{-4}$M.) and electrolysed at 25°. A plot of $E_{d.e.}$ against $\log_{10} I^a/(I_d - I)$ gives a straight line of slope = 0·031 (theory, 0·0296 v); similar agreement with theory is obtained on plotting data from Fig. 1. The half-wave potential obtained for $\simeq 10^{-4}$M-mercuric oxide agrees perfectly with the value for $\sim 10^{-4}$M-sodium hypochlorite (+0·10 v.). The hypochlorite second half-wave potential decreases from +0·122 (hypochlorous acid) to +0·099 v. (sodium hypochlorite), save for the anomalous result at 36·5% neutralisation. This shift agrees qualitatively with the theoretical displacement of 0·009 v. on doubling of the concentration of mercuric hydroxide at the electrode surface. Hypochlorous acid in the presence of an equivalent amount of nitric acid (Fig. 1, curve *A*) shows no mercuric oxide wave; the observed polarogram owes its origin to the electroreduction of equal quantities of mercurous nitrate and calomel.

The above interpretations of the hypochlorite double waves were confirmed by examining the products of complete reduction by metallic mercury of (*a*) 10^{-4}M-sodium hypochlorite in 0·1M-potassium nitrate and (*b*) 10^{-4}M-hypochlorous acid in 0·1M-potassium nitrate containing 0·2M-acetate buffer (pH 5·5). In each case the polarogram of the soluble reaction products closely resembled that obtained with a similar solution without previous chemical reduction.

The nature of the electrode processes, elucidated above, does not of course invalidate the analytical applications of the dropping mercury electrode in hypochlorite chemistry: the overall cathodic limiting currents remain proportional to the bulk concentration of hypochlorite up to 5×10^{-3}M.

The author is indebted to Mr. W. Nelson for the construction of the electrolysis cell.

EDWARD DAVIES CHEMICAL LABORATORIES, UNIVERSITY COLLEGE OF WALES, ABERYSTWYTH. [*Received, May 11th*, 1951.]

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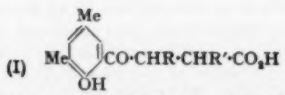
585. *Some Derivatives of Methylsuccinic Acid.*

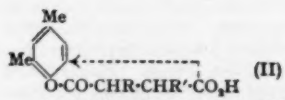
By WESLEY COCKER and A. K. FATEEN.

The *m*-4-xylyl hydrogen esters of methylsuccinic acid have been characterised, and the identity of the methyl-succinamic and -succinanilic acids established.

RECENTLY (*J.*, 1951, 929), it was shown that *m*-4-xylenol reacts with methylsuccinic anhydride to yield two esters: (A), m. p. 112—113°, obtained in the larger amounts, and (B), m. p. 65°, respectively. These were rearranged to give respectively (I; R = H, R′ = Me) and (I; R = Me, R′ = H).



(I)



(II)

(III) $H_2N{\cdot}CO{\cdot}CHR{\cdot}CHR'{\cdot}CO_2H$ $X{\cdot}CO{\cdot}CR{=}CR'{\cdot}CO_2H$ (IV)

The esters (A and B) have now been shown to be 2 : 4-xylyl β-carboxy-*n*-butyrate (II; R = H, R′ = Me) and 2 : 4-xylyl β-carboxy*iso*butyrate (II; R = Me, R′ = H) respectively. The esters were converted by alcoholic ammonia into the corresponding methylsuccinamic acids (III) which were identified by comparison with the methylsuccinamic acids obtained by catalytic reduction of the corresponding mesaconamic acids (IV; R = H, R′ = Me, X = NH_2: and IV; R = Me, R′ = H, X = NH_2) (Anschutz, *Annalen*, 1907, **353**, 139). The former unsaturated amide was obtained from the corresponding ester (IV; R = H, R′ = Me, X = OEt) (the α-ester of Anschutz, *loc. cit.*), and on reduction it gave β-carboxy-*n*-butyramide (III; R = H, R′ = Me). This compound melted at 125°. The methylsuccinamic acid obtained from A melted at 106—107° but, when the higher-melting amide was seeded with the lower, the melting point of the product was 106—107°. We consider that the two amides are chemically identical, and that we have encountered two forms of β-carboxy-*n*-butyramide. Both yield correct analyses, and both yield methylsuccinic acid on hydrolysis, and the higher-melting form depresses the melting point of the methylsuccinamic acid (m. p. 127°) obtained from B.

Morrell (*J.*, 1914, **105**, 2698) mentions a somewhat similar phenomenon in the case of one of the anilides obtained from methylsuccinic anhydride. This must be β-carboxy-*n*-butyranilide (see below). Crystallised from water, it melts at 143—145°; but crystallised from ethyl acetate, it melts at 159°, reverting to 143—145° on crystallisation once more from water. However, all attempts to interchange the melting points of the amide by crystallisation were unsuccessful.

The mesaconamic acid (IV; R = Me, R′ = H, X = NH_2) was obtained from the ester-chloride ($Cl{\cdot}CO{\cdot}CMe{=}CH{\cdot}CO_2Et$) by treatment with ammonia, followed by hydrolysis of the ester-amide with methanolic potassium hydroxide, a process worked out by Anschutz (*loc. cit.*). On reduction, it yielded β-carboxy*iso*butyramide (m. p. 125°) undepressed by the amide from B, but depressed by β-carboxy-*n*-butyramide.

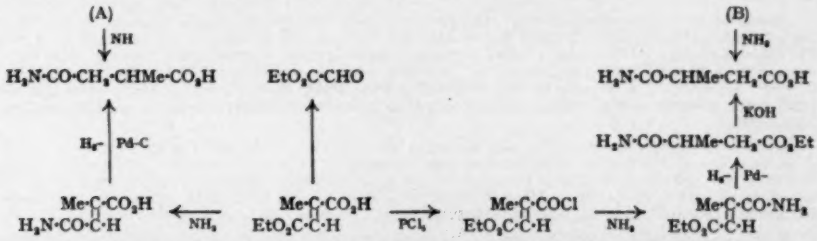
Assuming, therefore, that the mesaconamic ester (IV; R = H, R′ = Me, X = OEt) has the correct structure as given by Anschutz (*loc. cit.*), we feel justified in concluding that esters (A) and (B) have the structures suggested.

In the paper mentioned, Anschutz, revising his earlier views on the structure of the half-esters of mesaconic acid (Anschutz and Drugman, *Ber.*, 1897, **30**, 2649) claimed that partial hydrolysis of the diesters of mesaconic acid gives the " α-ester " (*e.g.*, ethyl β-carboxycrotonate, IV; R = H, R′ = Me, X = OEt), and that partial esterification of mesaconic acid gives a mixture in which the " α-ester " predominates.

The later paper of Anschutz is long and confusing and contains a number of printer's errors, but it appears that the half-esters were related, through their derivatives, to the known β-ester (β-carbethoxycrotonic acid; IV; R = Me, R′ = H, X = OEt) previously obtained by Cloez (*Compt. rend.*, 1890, **110**, 583) by treatment of ethyl γγ-dibromo-α-methylacetoacetate with barium carbonate. It is significant that Richter's " Organic Chemistry " (Allott, London, 1934, p. 572), in reporting Anschutz's work, interchanges the formulæ of the α- and the β-esters.

We have now identified, beyond doubt, the ester obtained by the partial hydrolysis of diethyl mesaconate as ethyl β-carboxycrotonate. This was accomplished by ozonolysis of the pure ester in sodium carbonate solution, ethyl glyoxylate being obtained and identified as its phenylhydrazone (Scheiber and Herold, *Ber.*, 1913, **46**, 1105). The claims made by Anschutz in his later paper are, therefore, correct.

The reactions we have performed are given in the scheme annexed.



When ester (A) was treated with aniline in methanol, it yielded a product which, by analogy with the corresponding amide, must be β-carboxy-*n*-butyranilide. It behaved as described by Morrell (*loc. cit.*). Its isomer, β-carboxy*iso*butyranilide, was obtained in a similar fashion from a mixture of (A) and (B), in which (B) predominated.

On theoretical grounds, the reaction of phenols, alcohols, and amines with unsymmetrical alkylsuccinic anhydrides would be expected to take place predominantly at the more electron-deficient carbonyl group, namely, the one further away from the alkyl; and with methylsuccinic anhydride, such has now been shown to be the case. It is, therefore, likely that the ester (m. p. 84—85°) obtained by Cocker, Fateen, and Lipman (*loc. cit.*) from *m*-4-xylenol and ethylsuccinic anhydride is 2 : 4-xylyl β-carboxy-*n*-valerate (II; R = H, R′ = Et).

The identity of the above *m*-4-xylyl hydrogen esters of methyl-, and ethyl-succinic acids and their *ortho*-rearrangement products in the Fries reaction (Cocker, Fateen, and Lipman, *loc. cit.*) having been established, it can be stated that rearrangement cannot take place by a process involving attack of the free carboxyl groups at the nucleus, as shown in (II).

In the Friedel–Crafts reaction between *m*-4-xylyl ethers and the above anhydrides, reaction takes place *meta* to the methoxy-group (cf. Cocker *et al.*, *J.*, 1950, 1781). At room temperature

the *meta*-position, activated by the two methyl groups, apparently offers the larger electron availability to the ion $-\overset{+}{C}O\cdot CHR\cdot CHR'\cdot CO_2H$. Some *meta*-migration may take place in the Fries rearrangement performed at 140°. The expected products of such rearrangements have not, however, been isolated, but the yield of pure *ortho*-compound never exceeded 45% of the theoretical. It is, therefore, not possible to draw any definite conclusion as to the mechanism of the Fries rearrangement of these esters, although intramolecular rearrangement involving π-complexes (Dewar, "Electronic Theory of Organic Chemistry," Oxford, 1949, p. 229) to a, possibly, thermally activated *ortho*-position, seems likely.

Experimental.

β-Carboxy-n-butyramide (III; R = H, R′ = Me).—The ester A (Cocker *et al.*, *J.*, 1951, 929) (11 g.) in methanol (80 c.c.) was saturated at room temperature with dry ammonia and left for 24 hours. Removal of alcohol under reduced pressure gave an oil, which was stirred with ether to remove xylenol; the residue was mixed with water and carefully acidified. The solution was then extracted continuously with ether, and the solid extract (5 g.) was crystallised several times from alcohol, from which the required *amide* was deposited as needles, m. p. 106—107° (Found: C, 45·6; H, 6·8. $C_5H_9O_3N$ requires C, 45·8; H, 6·9%).

β-Carboxyisobutyramide (III; R = Me, R′ = H) was similarly obtained from B (1·6 g.) as needles (0·58 g.), m. p. 127° (Found: C, 46·0; H, 7·0. $C_5H_9O_3N$ requires C, 45·8; H, 6·9%).

Ethyl β-carboxycrotonate (α-*Ester*) (IV; R = H, R′ = Me, X = OEt).—Mesaconic acid (*Org. Synth.*, 1931, **11**, 74) (20 g.) in anhydrous alcohol (120 c.c.) was saturated with hydrogen chloride and left overnight. Removal of solvent under reduced pressure, extraction with ether, and washing of the extract with sodium hydrogen carbonate solution yielded diethyl mesaconate (18·5 g.), b. p. 222°. The ester in alcohol (20 c.c.) was treated with a cold solution of potassium hydroxide (5·7 g.) in alcohol (68 c.c.). The solution became neutral in 45 minutes. The potassium salt which was deposited was collected and the filtrate was concentrated under reduced pressure, yielding a further quantity of the salt. The salt was dissolved in water (40 c.c.), extracted with ether to remove entrained starting ester (2·5 g.), and carefully acidified. The required ester was collected in ether, the solvent removed, and the product (12 g.; m. p. 60—66°) was crystallised from benzene as long needles, m. p. 67—68° (Anschutz, *Annalen*, 1907, **353**, 139).

β-Carboxycrotonamide (IV; R = H, R′ = Me, X = NH_2).—The previous compound (1·6 g.) was dissolved in ammonia (20 c.c.; *d* 0·880), then left for 48 hours, and the solution evaporated to dryness under reduced pressure. The solid was washed with alcohol; the ammonium salt of the required amide, m. p. 174—176°, remained, from which the amide itself (1·2 g.) (Anschutz, *loc. cit.*) was obtained, m. p. 222°.

Reduction of β-carboxycrotonamide. The previous compound (0·5 g.) in glacial acetic acid (100 c.c.) with palladised charcoal (0·5 g.) was quantitatively hydrogenated at atmospheric pressure for 4 hours. Filtration and removal of solvent, under reduced pressure, gave a product (0·4 g.) which, after crystallisation from alcohol, gave needles, m. p. 124—125° (Found: C, 45·6; H, 7·1. Calc. for $C_5H_9O_3N$: C, 45·8; H, 6·9%). A mixture of this material and the amide from (A) (m. p. 106°) melted at 106—107°, but a mixture of the hydrogenation product and β-carboxy*iso*butyramide (m. p. 127°) melted at 104—109°.

Ethyl β-Carbamylcrotonate.—This was obtained when the acid chloride of ethyl β-carboxycrotonate (Anschutz, *loc. cit.*) (0·3 g.) in ether (40 c.c.) was saturated at 0° with ammonia. Ammonium chloride was collected and the solvent was removed, yielding the required amido-ester which crystallised from the ether as plates, m. p. 78°. Attempts to hydrolyse this with methanolic potassium hydroxide to β-carbamylcrotonic acid failed, although Anschutz (*loc. cit.*) described a successful hydrolysis.

Reduction of ethyl β-carbamylcrotonate. The above ester (0·9 g.) was reduced in alcohol with palladised charcoal and hydrogen at atmospheric pressure. The reduction was complete in 18 hours. After removal of solvent, the product was refluxed with 5% methanolic potassium hydroxide (10 c.c.) for 2 hours. Methanol was then removed, the residue was diluted and acidified, and the mixture was shaken with ether from which an oil was obtained. On being rubbed with light petroleum, it solidified and melted at 92—104°. Extraction with benzene removed methylsuccinic acid, and the residue, after one crystallisation from alcohol, gave m. p. 125°, undepressed by the amide from (B).

β-Carboxy-n-butyranilide.—The ester A (2·8 g.) was set aside with aniline (4 g.) in methanol (5 c.c.) for 72 hours. The mixture was distilled in steam, the clear residue was acidified, and the solid product (1·1 g.) was collected and crystallised from water as prisms, m. p. 148°. Crystallisation from ethyl acetate gave plates, m. p. 158° (cf. Morrell, *loc. cit.*) (Found: C, 64·3; H, 6·4. Calc. for $C_{11}H_{13}O_3N$: C, 63·8; H, 6·3%).

β-Carboxyisobutyranilide.—A mixture of esters A and B (1·8 g.; m. p. 70—95°) was treated with aniline as above. An oil was obtained which solidified when rubbed with light petroleum. On extraction with chloroform, β-carboxy-*n*-butyranilide remained undissolved, and from the solvent a product, m. p. 120—132°, was obtained which, after several crystallisations from chloroform–light petroleum, gave the desired anilide (0·06 g.), m. p. 122° (cf. Morrell, *loc. cit.*).

Ozonolysis of Ethyl β-Carboxycrotonate.—The pure ester (1·9 g.) in water (20 c.c.) containing sodium carbonate (1·3 g.) was submitted to a stream of weakly ozonised oxygen for 3·5 hours, and the solution was then shaken in hydrogen with palladised charcoal. The filtered solution was extracted once with

ether, from which a small quantity of oil was obtained. This was treated with phenylhydrazine in acetic acid and ethyl glyoxylate phenylhydrazone (50 mg.), m. p. 120—124°, was obtained. One crystallisation from dilute alcohol raised the m. p. to 128° (Scheiber and Herold, *loc. cit.*), undepressed by authentic material obtained by ozonolysis of ethyl hydrogen maleate. A large amount of starting material remained unattacked.

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586. *Colouring Matters of the Aphididæ. Part V.* Infra-red Spectra.*

By A. W. JOHNSON, J. R. QUAYLE, T. S. ROBINSON, N. SHEPPARD, and A. R. TODD.

A detailed study of the infra-red spectra of the various aphins has been made; the erythroaphins from *Aphis fabæ*, *A. sambuci*, *Eriosoma lanigerum*, and *Myzus cerasi* have been found to give identical spectra, but those from *Tuberolachnus salignus* and *Sappaphis pyri* are each different from all the others so far examined. The spectra suggest that in all the erythroaphins the hydroxy-groups are strongly bonded with the quinone-carbonyl groups, *i.e.*, that the hydroxy-groups occupy *peri*-positions with respect to the quinone. Examination of the infra-red spectrum of diacetylerythroaphin further suggests that the quinone system in the erythroaphins is extended, *i.e.*, that the carbonyl groups are in different rings. No frequencies corresponding to non-bonded hydroxy- or carbonyl groups are present in the erythroaphin spectra, although both xanthoaphin and chrysoaphin appear to contain normal hydroxy-groups. Pyrolysis of erythroaphin at 230° gives acetic acid.

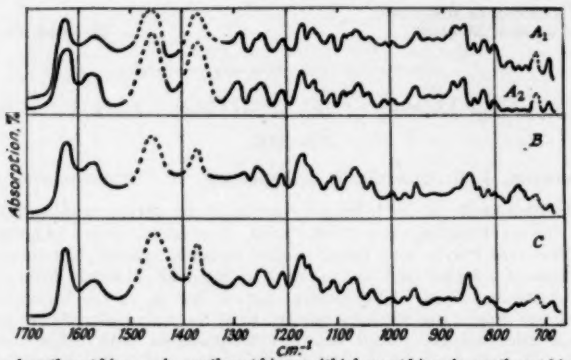
THE earlier papers of this series (Duewell, Human, Johnson, MacDonald, and Todd, *Nature*, 1948, **162**, 759; *J.*, 1950, 477, 485, 3304) have described the inter-relationships of the aphin colouring matters, isolated from a number of aphid species. Each series comprises a protoaphin which is the non-fluorescent pigment of the living insects, and a xanthoaphin, chrysoaphin, and erythroaphin, the last three fluorescent pigments being obtained progressively from protoaphin by enzymic action and acid treatment. The question whether there are several aphid species which yield identical aphins is one which has important implications, biological as well as chemical, and we have referred to this point in our previous publications. Up to the present, the species of origin has been indicated by the addition of a two-letter suffix to the name of the particular colouring matter, *e.g.*, erythroaphin-*fb* (from *Aphis fabæ*) or -*sl* (from *Tuberolachnus salignus*), and so on (Part I, *loc. cit.*). Obviously, the question of nomenclature would be simplified, as well as the problems of collection of raw material, if the pigments from all the various species had not always to be kept separate.

The experimental evidence described in this paper suggests that the pigments from *A. fabæ* (host: beans, etc.), *A. sambuci* (elders), *Eriosoma lanigerum* (apple trees), and *Myzus cerasi* (cherry trees) are almost certainly identical, but that those from *T. salignus* (willow trees) and *Sappaphis pyri* (pear trees) are each unique. Information on the aphins from other species will be presented as it becomes available. It seemed probable from the evidence presented in Parts II and III that the aphins from *A. fabæ* were not identical with those from *T. salignus*, although they were undoubtedly very similar. The corresponding aphins of the two series were indistinguishable on the basis of visible and ultra-violet spectra and no means are known to us at present for the separation of mixtures of the corresponding pigments, *e.g.*, the erythroaphins-*fb* and -*sl*. Although erythroaphin-*fb* and erythroaphin-*sl* had the same or very similar molecular formulæ as far as could be judged from elementary analyses, and the same applied to the two chrysoaphins, the carbon and hydrogen figures for xanthoaphin-*fb* and xanthoaphin-*sl* differed considerably. Repetition of the isolation and analyses of the xanthoaphins has demonstrated that these compounds retain traces of solvents very tenaciously and, as they

* Part IV, *J.*, 1950, 3304.

are unstable to heat, the problem of solvent removal is more difficult than usual. The figures obtained for the carbon content of xanthoaphin-*sl* in the present work are much closer to those of xanthoaphin-*fb* previously reported, although consistent analyses on different batches of xanthoaphin-*sl* have still not been obtained. The retention of solvent seems to offer the most logical explanation of this phenomenon but there still remains the possibility that xanthoaphin

FIG. 1.

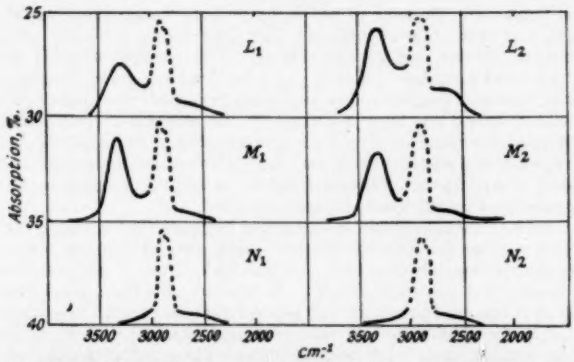


In,ra-red spectra of erythroaphins. A_1, *erythroaphin-*sm (*thick sample*); A_2, *erythroaphin-*fb (*thin sample*); *B, erythroaphin-*sl; *C, erythroaphin-*py. *The spectra of erythroaphins-*ln *and -*ce *are identical with* A_1 *and* A_2.

may contain varying amounts of an undetected impurity. A formula, $C_{30}H_{28}O_{12}$, is favoured at present for xanthoaphin-*sl*, compared with $C_{30}H_{30}O_{11}$ for xanthoaphin-*fb*, but it is emphasised that these provisional molecular formulæ may well have to be amended later.

Small but significant differences between the aphin-*fb* series and the *sl* series were apparent in their solubilities, their behaviour on heating (the *sl* series decomposed on melting), their crystalline habits, and in the yields of mellitic acid obtained from the nitric acid oxidation of

FIG. 2.



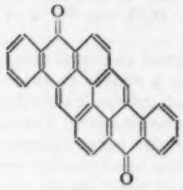
Hydroxyl region of infra-red spectra of aphins. L_1, *xanthoaphin-*fb; L_2, *xanthoaphin-*sl; M_1, *chrysoaphin-*fb; M_2, *chrysoaphin-*sl; N_1, *erythroaphin-*fb; N_2, *erythroaphin-*sl.

the erythroaphins, that from the *fb* pigment (and *ce*, Part IV, *loc. cit.*) being appreciably smaller than that from erythroaphin-*sl*. A study of the infra-red spectra of a variety of aphin pigments from different species has confirmed the difference between the *fb* and *sl* series and at the same time has shed a little more light on the structures of the pigments.

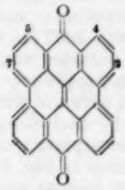
The infra-red spectra of the erythroaphins-*fb*, -*sm*, -*ln*, -*ce*, -*sl*, and -*py* (Figs. 1 and 2) were determined and a general survey of the spectra leaves no doubt as to the close relationship

between these compounds. Well-defined maxima are observed near 1625, 1575, 1290, 1260, 1210, 1170, 1115, 1070, 955, 855, and 820 cm.$^{-1}$ in all of the spectra. The four erythroaphins-*fb*, -*sm*, -*in*, and -*ce* give spectra which are identical in every detail, and the first two of these are shown in Fig. 1. It therefore seems reasonable to deduce that they are identical substances. The spectra of the erythroaphins-*sl* and -*py* differ from the others in several details and in particular they have an extra distinct absorption at 975 cm.$^{-1}$ and lack a strong absorption at 880 cm.$^{-1}$. Only erythroaphin-*sl* shows a marked absorption band at 760 cm.$^{-1}$. These erythroaphin spectra were in the first instance considered in relation to the chemical evidence, cited in Parts II and III (*locc. cit.*) for the presence of quinonoid carbonyl groups and two phenolic hydroxyl groups in the erythroaphin-*fb* and -*sl* molecules.

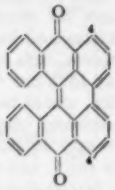
The quinonoid grouping in the molecule would be expected to give rise to a strong absorption band corresponding to the stretching mode of the carbonyl group. The carbonyl frequencies of *p*-benzoquinone and anthraquinone have been given by Flett (*J.*, 1948, 1441) as 1660 and 1676 cm.$^{-1}$ respectively. As part of this investigation we have also observed the corresponding absorption band of 1 : 4-naphthaquinone at 1664 cm.$^{-1}$, and it seems from this limited evidence that simple *p*-quinones might be expected to absorb in the approximate region 1660—1680 cm.$^{-1}$. Josien and Fuson (*J. Amer. Chem. Soc.*, 1951, **73**, 478) have observed the carbonyl absorption bands of the extended quinones, 3 : 8- and 3 : 10-pyrenequinone, at 6·1 μ or approximately 1640 cm.$^{-1}$, and a further series of extended quinones has been studied spectroscopically in this laboratory (Hadzi and Sheppard, *J. Amer. Chem. Soc.*, in the press). The values found for the carbonyl absorption bands were as follows, only the strong absorption band with the highest frequency in the range 1550—1750 cm.$^{-1}$ being quoted in each case: pyranthrone (I), 1655 cm.$^{-1}$; *meso*naphthadianthrone (II), 1649 cm.$^{-1}$; helianthrone (III), 1646 cm.$^{-1}$; 1 : 2 - 6 : 7-dibenzopyrene-3 : 8-quinone (IV), 1645 cm.$^{-1}$; dibenzanthrone (V), 1638 cm.$^{-1}$; and diphenoquinone (VI), 1626 cm.$^{-1}$. It can be seen that the majority of these extended quinones have their carbonyl absorptions in the range 1655—1635 cm.$^{-1}$, a single exception being diphenoquinone with the frequency of 1626 cm.$^{-1}$. However, because of the unusual structure and chemical reactivity of the latter molecule it cannot be regarded as typical.



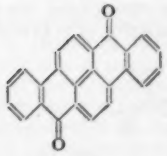
(I.)



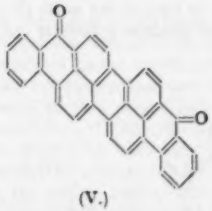
(II.)



(III.)



(IV.)



(V.)

(VI.)

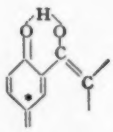
The observed value of the "carbonyl" frequency in the erythroaphin spectra is at 1625 cm.$^{-1}$, and it can be seen to be at the extreme lower end of the above range found for quinones and considerably lower than the frequencies found for the majority of simple or extended quinones. If this absorption band in the erythroaphin spectra is to be correlated with the presence of quinonoid carbonyl groups, it therefore appears that these are likely to be in unusual structural surroundings.

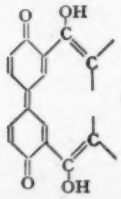
A second important feature of the erythroaphin spectra is apparent when consideration is given to the features to be expected from the presence of phenolic hydroxyl groups. Usually such groups give rise to strong and broad absorption bands near 3300 cm.$^{-1}$ which arise from

the stretching mode of the hydroxyl linkages, but none of the erythroaphin spectra has absorption bands in this region (see Fig. 2). However, there is now considerable evidence in the literature that both the carbonyl and the hydroxyl absorption bands are shifted markedly to lower frequencies when these two groups form chelated six-membered ring systems by means of hydrogen bonding (Gordy, *J. Chem. Physics*, 1940, **8**, 516; Flett, *loc. cit.*; Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068; Hinsberger, *ibid.*, 1950, **72**, 5626). Flett's work on the infra-red spectra of a series of hydroxyanthraquinones is particularly relevant and has shown that the presence of a β-hydroxy-group in the nucleus, where no intramolecular hydrogen bonding with the quinonoid carbonyl is possible, gives rise to normal carbonyl and hydroxyl frequencies near 1675 and 3350 cm.$^{-1}$ respectively. However, an α-hydroxy-group which can form a six-membered chelate ring with the quinone carbonyl invariably causes the appearance of a low carbonyl frequency in the range 1590—1640 cm.$^{-1}$, to be compared with 1676 cm.$^{-1}$ in the unsubstituted quinone, while the usual hydroxyl absorption band does not appear. The apparent lack of a hydroxyl absorption in the case of the α-hydroxyanthraquinones is almost certainly due to the fact that the very strong hydrogen bonding has caused the absorption band to occur at low frequencies in the OH absorption region near 3000 cm.$^{-1}$ in the form of a much broader band of lower peak intensity. We have re-investigated the spectra of 1-hydroxy-, 1 : 4-dihydroxy-, and 1 : 5-dihydroxy-anthraquinone originally studied by Flett (*loc. cit.*) and found a weak and broad absorption band centred near 2700 cm.$^{-1}$, in agreement with the above hypothesis. We have also made further observations on the infra-red spectra of extended quinones to include certain of the hydroxy-derivatives. Once again it was found that hydroxyl groups in α-positions caused lowering of the quinonoid carbonyl frequencies, and that when only such α-hydroxyl groups were present the *ca.* 3300-cm.$^{-1}$ absorption band could not be detected. The effect on the carbonyl frequency is well illustrated by the positions of these absorption bands in the following derivatives of *meso*-naphthadianthrone, only the absorption band with the highest frequency in the range 1550—1750 cm.$^{-1}$ being quoted in each case as before: *meso*naphthadianthrone, 1649 cm.$^{-1}$; 4 : 4′-dihydroxy*meso*naphthadianthrone (Attree and Perkin, *J.*, 1931, 144), 1620 cm.$^{-1}$; 2 : 2′-dimethyl-4 : 4′ : 5 : 5′ : 7 : 7′-hexahydroxy*meso*naphthadianthrone (hypericin; Brockmann, von Falkenhausen, and Dorlas, *Naturwiss.*, 1950, **37**, 540), 1589 cm.$^{-1}$; and also in the case of helianthrone and its substitution products: helianthrone, 1646 cm.$^{-1}$; 4 : 4′-dihydroxy-helianthrone (Attree and Perkin, *loc. cit.*), 1607 cm.$^{-1}$.

From the above data it can be concluded that the observed carbonyl frequency of the erythroaphins at 1625 cm.$^{-1}$, while abnormally low in value for a simple or extended quinone group in isolation, would be consistent with the presence of such groups if they formed part of chelated six-membered rings caused by hydroxy-groups in neighbouring α-positions. Such a formulation would at the same time explain the absence of the usual hydroxyl stretching mode near 3300 cm.$^{-1}$, and as can be seen in Fig. 2 there is some spectroscopic evidence for a weak and very broad absorption band centred near 2700 cm.$^{-1}$ which would be expected to replace the former absorption under such conditions. Thus, the spectroscopic evidence strongly suggests the presence of two of the units (VII) in the erythroaphins, the substituents on C* depending on whether the quinone system is contained in one ring or is extended. When

(VII.)





(VIII.)

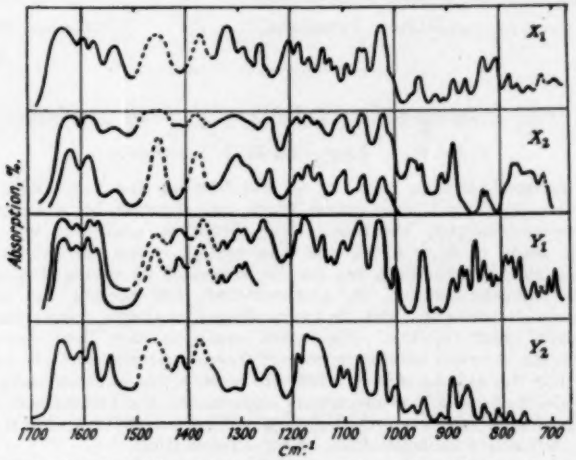
the hydroxy-groups of the hydrogen-bonded hydroxy-quinones are acetylated, the hydrogen bonding is destroyed and the position of the carbonyl absorption in the acetoxy-quinones reverts to a value comparable with that of the parent quinone (Flett, *loc. cit.*). In the case of erythroaphin-*sl*, the diacetyl derivative (Part III, *loc. cit.*) shows a carbonyl absorption band at 1637 cm.$^{-1}$ (in addition to an extra band near 1770 cm.$^{-1}$ due to the acetoxy-group) which strongly suggests the presence of an extended quinone system in erythroaphin-*sl*. Chemical evidence to support this deduction will be presented in a later paper. The available

infra-red data do not allow a choice of the type of extended quinone system present but the simplest expression of the facts so far presented would be the grouping (VIII).

Another property of the erythroaphins-*fb* and -*sl* can be considered in the light of the infra-red spectra. It has been found that at 230° in an atmosphere of nitrogen or *in vacuo*, the erythroaphins evolve 0·5—0·6 mole of acetic acid. Although at first we were inclined to interpret this result as indicating the presence of an inert acetoxy-group in erythroaphin (quantitative hydrolyses of diacetylerythroaphin and tetra-acetyldihydroerythroaphin indicate the presence of two and four acetyl groups respectively), the absence of evidence for any " normal " (*i.e.*, not hydrogen-bonded) carbonyl groups on the basis of the infra-red spectrum (a strong absorption band in the region of 1780—1750 cm.$^{-1}$ would be expected) renders this explanation improbable. The acetic acid must therefore arise from a more extensive thermal decomposition but the nature of the other products of the reaction has not yet been ascertained.

The infra-red spectra of the xanthoaphins-*fb* and -*sl* and of the corresponding chrysoaphins are shown in Figs. 2 and 3. They all show strong absorption bands in the region 1640—1620 cm.$^{-1}$ which can probably be correlated with the presence of carbonyl groups of extended

FIG. 3.



Infra-red spectra of xanthoaphins and chrysoaphins. X_1, *xanthoaphin*-fb; X_2, *xanthoaphin*-sl; Y_1, *chrysoaphin*-fb; Y_2, *chrysoaphin*-sl.

quinones. For xanthoaphin-*sl* the highest frequency in this region is, as for the erythroaphins, at 1625 cm.$^{-1}$, suggesting that in this case both the quinonoid carbonyls are chelated. In agreement with this hypothesis, xanthoaphin-*sl* has a particularly marked broad absorption centred near 2700 cm.$^{-1}$ attributable to the stretching frequency of chelated hydroxyl bonds. Xanthoaphin-*fb* also has an absorption band in this region and similar, but weaker, features seem also to be present in the chrysoaphin spectra. Unlike the erythroaphins, the xanthoaphins exhibit strong absorption bands between 3300 and 3400 cm.$^{-1}$ (Fig. 2) which provide good evidence for the presence of additional hydroxyl groups of the normal type such as occur in the spectra of alcohols and phenols. In the region 1600—700 cm.$^{-1}$ there are several strong absorption bands common to the spectra of the two chrysoaphins, *viz.*, near 1415, 1170, 1070, 1030, 1000, and 950 cm.$^{-1}$ which show that they are closely related substances. There are fewer coincidences between the spectra in this region for the xanthoaphins-*fb* and -*sl* and this is in agreement with the chemical evidence cited above that these two substances are of rather different structure. The spectra, however, still maintain a strong general resemblance.

EXPERIMENTAL.

Spectroscopic Methods.—The infra-red spectra of the aphins were run as mulls in Nujol prepared from the crystalline materials. The infra-red spectrometers used were of the Perkin–Elmer 12B and Hilger D209 types used with rock-salt prisms under standard conditions (Sheppard and Sutherland, *J.*, 1947, 1540).

Xanthoaphin-sl.—Prepared as described in Part III (*loc. cit.*) and crystallised, as before, from ether–carbon tetrachloride it had m. p. 210° (decomp.) (Found, in material dried at room temperature: C, 62·4, 62·45, 63·0, 63·7; H, 4·7, 4·8, 4·6, 4·7. $C_{30}H_{28}O_{12}$ requires C, 62·1; H, 4·6. $C_{30}H_{28}O_{12}$ requires C, 62·4; H, 4·5%). A further sample was crystallised from ether–benzene (Found, in material dried at room temperature: C, 67·7, 68·0; H, 5·25, 5·2. $C_{30}H_{28}O_{12},2C_6H_6$ requires C, 68·5; H, 5·5%).

Pyrolytic Decomposition of Erythroaphin.—Erythroaphin-*fb* (104 mg.) was introduced into a small hard-glass test-tube and a pad of purified asbestos placed over the pigment. The test-tube was sealed on to a length of glass tubing leading into a liquid-air trap and the whole evacuated and sealed. The pigment was then heated at 230° for 8 hours, after which the tube was opened and the distillate treated with piperazine hexahydrate. The resulting piperazine salt was repeatedly washed with ether, crystallised from *n*-butanol, sublimed, and then recrystallised as before; it had m. p. 204°, alone and mixed with an authentic specimen of piperazine acetate. An identical product was obtained from the pyrolysis of erythroaphin-*sl*. In further experiments the acetic acid so obtained was determined by direct titration with standard alkali. From erythroaphin-*fb* there was obtained 0·60 mole of acetic acid, and from erythroaphin-*sl* 0·54 mole.

Grateful acknowledgment is made to the Royal Commissioners for the 1851 Exhibition for a Senior Studentship (to N. S.) and to the University of Wales for a Fellowship (to J. R. Q.). We are also indebted to Dr. S. F. MacDonald for helpful discussions, to Drs. B. R. Brown, H. Duewell, and J. P. E. Human for assistance in the preparation of certain of the aphins and polycyclic quinones, and to Mr. D. Hadži for some of the spectroscopic determinations.

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587. *The Polarographic Reduction of Some Aminoacridines.*

By R. C. KAYE and H. I. STONEHILL.

In aqueous solution, 1-, 2-, 3-, 4-, and 5-amino- and 2 : 7- and 2 : 8-diamino-acridines yield polarograms which are distorted by adsorption at the dropping-mercury electrode. The adsorption, confirmed by oscillographic study of the current–time relationship, is less marked than for acridine, and, as with the latter, may be eliminated by adding ethanol. In aqueous-ethanolic solution, the aminoacridines, like acridine, are reduced in two one-electron steps, with the intermediate formation of a semiquinone of apparently great stability. Theoretical equations have been derived to describe the observed relation between half-wave potential and pH for each step. For the aminoacridines which are most active antibacterially (*viz.*, the 2-, 5-, 2 : 7-, and 2 : 8-substituted compounds), the first reduction step requires no hydrogen ions at the biologically important pH of 7; this is not so for the less active aminoacridines, or for acridine itself.

RECENT work (Kaye and Stonehill, *J.*, 1951, 27) on the polarographic reduction of acridine is now extended to a series of aminoacridines, with the aim of correlating electro-reduction characteristics with bacteriostatic activity.

EXPERIMENTAL.

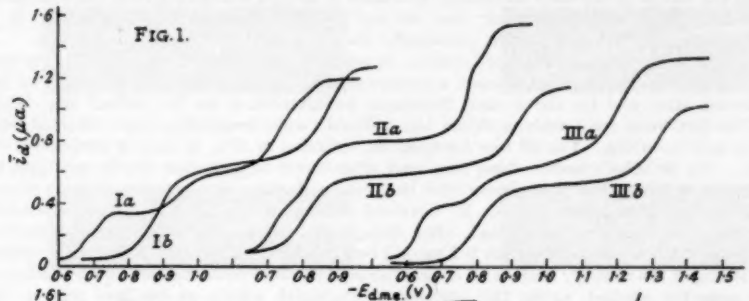
1-, 2-, 3-, and 4-Aminoacridines were samples prepared by Albert and Ritchie (*J. Soc. Chem. Ind.*, 1941, **60**, 120) and kindly presented by Mr. C. L. Bird of Leeds University. Medicinally pure 5-, 2 : 7-, and 2 : 8-amino-substituted acridines were further purified by several recrystallisations from water.

Ethyl alcohol, buffers, apparatus, and experimental technique were as described previously (*J.*, 1951, 27).

RESULTS AND DISCUSSION.

(i) *Detection and Suppression of Adsorption.*—Figs. 1—2 show typical polarograms for all the compounds studied, the same buffer mixture being used as supporting electrolyte in both aqueous and 50% (by volume) aqueous-alcoholic solutions. For 2 : 8-diaminoacridine (Fig. 2, Curves IV) all the polarograms for aqueous solutions (concentration range, 1—8 × 10^{-4} M; pH range 0—14; 10% of alcohol included in solutions at pH >8 where the free base is almost water-insoluble) are anomalous, although less so than those of acridine. Two main reduction waves are identifiable, together with a small anomalous after-wave on the first step, and in some cases a smaller fore-wave on the second step. At the higher concentrations, and over the potential range corresponding to the after-wave on the first main step, abnormal galvanometer oscillations

were observed during polarography, similar to those found with acridine. On the inclusion of 50% of alcohol in the solvent, the anomalies disappeared. The anomalous after-wave on the first step may be attributed, on Brdička's theory (*Z. Elektrochem.*, 1942, **48**, 278), to adsorption of unreduced 2 : 8-diaminoacridine on the dropping-mercury electrode, which is suppressed by the addition of alcohol. Supporting evidence is provided by the oscillographic records (Fig. 3, *A*—*I*) of the current-time relationship during the first 2 seconds of the life of a single mercury drop. These oscillograms are lettered to correspond with Fig. 2 (Curve IV*a*). For potentials outside the range *A*—*F* (Fig. 3), normal oscillograms are obtained. Between the potentials of *A* and *F* the current, immediately after the fall of a mercury drop, first rises with abnormal rapidity; this is probably due to adsorption hastening the normally solely diffusion-controlled supply



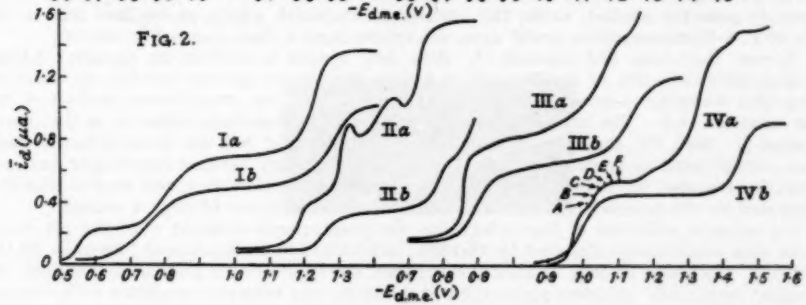


FIG. 1.

Polarograms in (a) *water and* (b) 50% *alcohol.*

I. 1-*Aminoacridine*, 4 × 10^{-4}M; (a) pH 7·38, (b) pH 8·29.
II. 2-*Aminoacridine*, 4 × 10^{-4}M; (a) pH 7·38, (b) pH 8·29.
III. 3-*Aminoacridine*, 4 × 10^{-4}M; (a) pH 7·38, (b) pH 8·29.

FIG. 2.

Polarograms in (a) *water and* (b) 50% *alcohol.*

I. 4-*Aminoacridine*, 4 × 10^{-4}M; (a) pH 7·38, (b) pH 8·29.
II. 5-*Aminoacridine*, 2 × 10^{-4}M; (a) pH 9·07, (b) pH 10·39.
III. 2 : 7-*Diaminoacridine*, 4 × 10^{-4}M; (a) pH 7·38, (b) pH 8·29.
IV. 2 : 8-*Diaminoacridine*, 2 × 10^{-4}M; (a) pH 7·38, (b) pH 8·29 (*current scale half that shown*).

of reducible material to the electrode surface. After reaching a maximum, the current then falls slightly, probably because adsorption has caused a temporary depletion of reducible; material in the solution near the dropping-mercury electrode. This is eventually made good by diffusion from the bulk of the solution, whereupon the current finally rises slowly. Oscillograms *C*, *G*, *H*, and *I* (Fig. 3) all refer to a fixed electrode potential (−1·054 v against the saturated calomel electrode), and illustrate the effects of the addition of increasing amounts of alcohol to the supporting electrolyte (current amplification is lower for *C* than for *G*, *H*, or *I*). Clearly 20% of alcohol does not prevent adsorption, 50% does not quite, and 60% does almost completely eliminate it. Since the polarogram with 50% alcohol shows no adsorption anomalies, it is evident that slight adsorption is undetectable polarographically,

and that the oscillogram provides the more reliable evidence of adsorption. The adsorption of 2 : 8-diaminoacridine on the dropping-mercury electrode is weaker than that of acridine, as shown by the less pronounced polarographic anomalies and the complete suppression of adsorption by a lower alcohol concentration. Apart from the complication due to the adsorption's being of semiquinone and not of unreduced material in the case of acridine, this is to be expected when the molecule is made more hydrophilic by the introduction of two amino-groups, and accords with the observation (Albert, Goldacre, and Heyman, *J.*, 1943, 651) that acridine and 2 : 8-diaminoacridine are respectively the most and the least hydrophobic and surface-active of a series of acridines.

2 : 7-Diaminoacridine also gives a small anomalous after-wave on the first main reduction step at all pH values in aqueous solutions; inclusion of 50% of alcohol removes the anomalies (Fig. 2, Curves III). Brdička's theory (*loc. cit.*) and the current–time oscillogram (Fig. 3, *J*) suggest that, as with the 2 : 8-isomer, principally the unreduced compound is adsorbed.

1-, 2-, 3-, and 4-aminoacridine were studied, in aqueous solution, only at pH 7·38, because of the scarcity of materials. In all cases a pronounced anomalous fore-wave occurred on the first reduction step, and for the 1- and 2-isomers, an after-wave on the second step (Figs. 1—2). The fore-wave for 1-aminoacridine was a double wave resembling that obtained with acridine in acid solutions. For all four compounds, inclusion of 50% of alcohol eliminated the anomalies. On Brdička's theory, these fore- and after-waves suggest that chiefly semiquinone is adsorbed, as with acridine (it is shown later that both reduction steps are one-electron steps). The current–time oscillogram (Fig. 3, *K*) obtained during the reduction of 4-aminoacridine supports this view, since it shows that, after detachment of the mercury drop, the current stays at the minimum value for about 0·1 second before starting to grow; this is presumably due to blocking of the mercury surface by some adsorbate which is not reducible at the particular electrode potential applied, unlike the unreduced compound, which, as we have seen in the case of 2 : 8-diaminoacridine, would upon adsorption cause a sharp increase in current.

Breyer, Buchanan, and Duewell (*J.*, 1944, 360) sought to explain the apparent 3-stage polarographic reduction of acridine and of 4-aminoacridine in aqueous solution by assuming compound formation between the unreduced material and the semiquinone product of the first reduction step. The foregoing evidence shows that for 4-aminoacridine, as in the case of acridine (*J.*, 1950, 27), this interpretation is incorrect, and that two, not three, reduction steps occur, complicated by adsorption. The lack of proportionality between step height and concentration reported by these workers is due to adsorption complications, and we find that it is eliminated for the aminoacridines, as with acridine, on the inclusion of 50% of alcohol.

For aqueous solutions of 5-aminoacridine the polarograms obtained over the pH range 0—14 were considerably distorted by maxima, in addition to an anomalous fore-wave on the first step. Inclusion of 50% of alcohol suppressed the fore-wave but only partly removed the maxima; practically complete suppression of the latter was achieved by adding 0·1% methyl cellulose to the 50% alcoholic solution, and restricting the concentration of 5-aminoacridine to 2×10^{-4}M.

(ii) *Semiquinone Formation.*—Breyer, Buchanan, and Duewell (*loc. cit.*) applied the Ilkovič equation (*Coll. Czech. Chem. Comm.*, 1934, **6**, 498) $\bar{i}_d = 605\ nD^{\frac{1}{2}}m^{\frac{2}{3}}t^{\frac{1}{6}}c$ to show that acridine and several of its amino-derivatives were reduced at the dropping-mercury electrode in two one-electron stages (i_d = mean diffusion current in amperes, n = number of electrons

TABLE I.

Aminoacridine.	c (millimol./l.)	First step $\bar{i}_d$ (μa.)	First step n	Second step $\bar{i}_d$ (μa.)	Second step n	$-E_1$ [b,c]	$-E_2$ [b,c]	$E_{\frac{1}{2}}$ [b,c]	log $\sqrt{K}$ [b]
1-	0·4	0·53	1·09	0·54	1·13	0·748	1·350	0·301	5·10
2-	0·4	0·49	1·00	0·45	0·94	0·760	1·328	0·334	5·65
3-	0·4	0·48	0·98	0·42	0·88	1·724	1·230	0·253	4·29
4-	0·2	0·22	0·90	0·25	1·04	—	—	—	—
	0·4	0·43	0·88	0·48	1·00	0·650	1·220	0·285	4·85
5- [a]	0·2	0·24	0·99	0·28	1·17	1·210	1·607	0·198	3·36
Diaminoacridine.									
2 : 7-	0·2	0·24	0·98	0·25	1·04	—	—	—	—
	0·4	0·46	0·94	0·48	1·00	0·840	1·252	0·208	3·52
2 : 8-	0·2	0·22	0·90	0·22	0·92	—	—	—	—
	0·4	0·44	0·90	0·46	0·96	1·007	1·362	0·177	3·00

[a] At pH 10·39 (in 50% alcohol). [b] At pH 7·0 (in 50% alcohol).
[c] In volts against the Saturated Calomel Electrode.

FIG. 3.

(*A*) — 1·022 mv

(*B*) — 1·037 mv

(*C*) — 1·054 mv

(*D*) — 1·068 mv

(*E*) — 1·080 mv

(*F*) — 1·107 mv

(*G*) — 1·054 mv

(*H*) — 1·050 mv

(*I*) — 1·054 mv

(*J*)

(*K*)

[*To face p. 2640.*

involved per molecule, D = diffusion coefficient of the reducible molecule in cm.^{2}sec.$^{-1}$, m = mercury flow rate in mg./sec., t = drop time in sec., and c = concentration in millimol./l.). Since adsorption at the dropping-mercury electrode in aqueous solutions might invalidate the Ilkovič equation, which is derived on the assumption that diffusion alone controls the supply of electro-active material to the electrode, we have recalculated n, Ilkovič's equation being

FIG. 4.

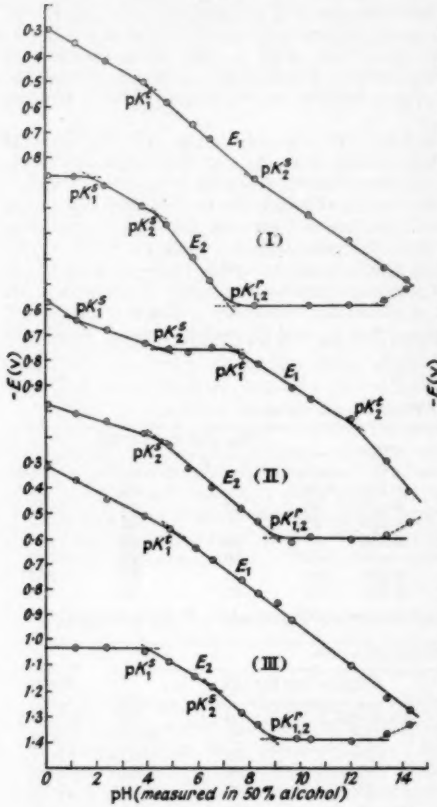


FIG. 5.

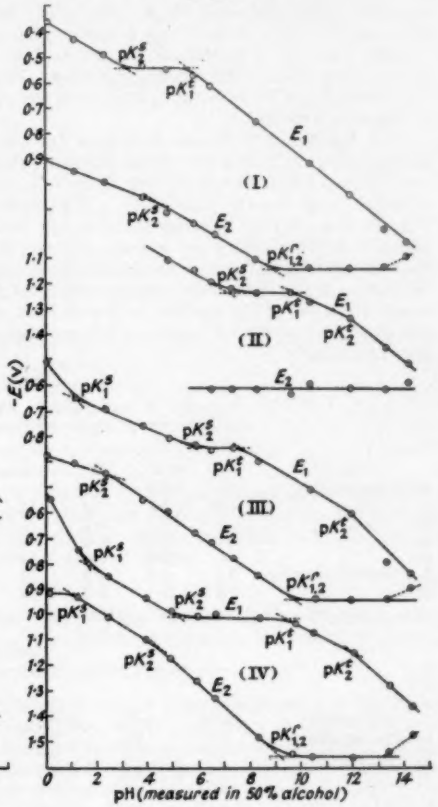


FIG. 4.

Variation with pH *of the half-wave potentials,* E_1 *and* E_2, *in 50% alcohol.*

I. 1-*Aminoacridine,* 4×10^{-4}M. *II.* 2-*Aminoacridine,* 4×10^{-4}M.
III. 3-*Aminoacridine,* 4×10^{-4}M.

FIG. 5.

Variation with pH *of the half-wave potentials,* E *and* E_2, *in 50% alcohol.*

I. 4-*Aminoacridine,* 4×10^{-4}M. *II.* 5-*Aminoacridine,* 2×10^{-4}M.
III. 2 : 7-*Diaminoacridine,* 4×10^{-4}M. *IV.* 2 : 8-*Diaminoacridine,* 4×10^{-4}M.

used, for 50% alcoholic solutions of the aminoacridines, in which adsorption is insufficient to distort polarograms. The values used for m and D (taken to be the same as for acridine) were as reported previously (*J.*, 1950, 27); t values appropriate to each half-wave potential were employed. The resulting n values, given in Table I, refer to the single pH of 8·29 (measured in 50% alcohol), but they apply over the pH range 0—14 since wave-heights were practically independent of pH within experimental error, except for 5-aminoacridine, for which incipient

maxima caused significant pH-variation of wave-height, and an overlapping hydrogen wave at pH $<4{\cdot}8$ rendered the recording of the two waves impossible. Table I shows that the aminoacridines, like the parent compound, are reduced in two one-electron stages, with the intermediate formation of a semiquinone radical. The half-wave potentials E_1 and E_2 of the first and second steps, respectively, for pH 7·0 in 50% alcohol, the index potential, which for well-separated waves is given by $E_i = \frac{1}{2}(E_1 - E_2)$, and the value of log K (K = apparent semiquinone formation constant) are also given in Table I. Values of K were calculated from the equation (Michaelis, *Ann. N.Y. Acad. Sci.*, 1940, **40**, 39) $\sqrt{K} = 10^{E_i/0{\cdot}059} - 3 \times 10^{-E_i/0{\cdot}059}$, which applies only to reversible systems, whereas logarithmic analysis (Kolthoff and Lingane, "Polarography," Interscience Publishers Inc., New York, 1946, p. 154) shows that all the polarograms refer to irreversible processes. Nevertheless, the large K values suggest that the semiquinones are highly stable, and, as in the case of acridine, we shall regard K as a measure of apparent stability.

(iii) *Relationships between Half-wave Potentials and* pH.—In view of the variation with pH of the biological properties of the aminoacridines (Albert *et al.*, *Brit. J. Exp. Path.*, 1945, **26**, 160), we have determined E_1 and E_2 in 50% aqueous-alcoholic solutions at several pH values over the range 0—14 (Figs. 4—5). The similar results obtained by Breyer, Buchanan, and Duewell (*loc. cit.*) for aqueous solutions are less complete and are complicated by adsorption effects. In interpreting our results, we may note the generalisation made by Clark (*Chem. Reviews*, 1925, **2**, 127) that, as pH increases, the graph of normal redox potential against pH exhibits a fairly sharp bend corresponding to algebraic decrease (increase) of slope at a pH equal to the pK of the oxidised (reduced) form of the system concerned. This is confirmed by the equations developed below on the assumption that E_1 and E_2 may be treated as normal redox potentials.

TABLE II.

	From E_1–pH curve.								
						Slope in mv for pH			
Compound	pK_1^s	pK_2^s	pK_1^t	pK_2^t	$-E_1^{o'}$ (v)	$<$pK_1^t	pK_1^s—pK_2^t	pK_1^t—pK_2^t	$>$pK_2^t
1-Aminoacridine ...	—	8·2	3·8	—	0·295	57 [a]	—	87 [c]	67 [d]
2- ,, ...	1·2	4·6	7·4	12	0·570	65	35	60	118
3- ,, ...	—	—	5·1	—	0·320	52 [a]	—	78 [b]	—
4- ,, ...	—	3·2	5·6	—	0·360	—	59	80 [b]	—
5- ,, ...	—	7·4	9·6	12	—	—	58	44	80
2 : 7-Diaminoacridine	1·2	5·8	7·3	12	0·500	120	43	58	103
2 : 8- ,,	1·4	5·0	9·3	12	0·520	180	60	50	88

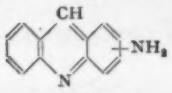
[a] For pH $<$ pK_1^t. [b] for pH $>$ pK_1^t. [c] For pH between pK_1^t and pK_2^s. [d] For pH $>$ pK_2^s.

	From E_2–pH curve.						
				Slope in mv for pH			Electrometric
Compound	pK_1^s	pK_2^s	p$K_{1',2}^r$	pK_1^s—pK_2^s	pK_2^s—p$K_{1',2}^r$	$-E_2^{o'}$ (v)	pK_1^t (at 20°)
1-Aminoacridine ...	1·7	4·5	7·3	57	127	0·887	3·59
2- ,, ...	—	4·4	9·0	30	83	0·970	7·61
3- ,, ...	4·0	6·3	8·9	59	86	1·036	5·03
4- ,, ...	—	4·7	8·9	38	60	0·904	5·50
5- ,, ...	—	—	—	—	—	—	9·45
2 : 7-Diaminoacridine	—	2·5	9·8	35	67	0·870	7·74
2 : 8- ,,	1·0	4·5	9·1	60	85	0·920	9·50

The general form of the E_1–pH curve is similar for the 2-, 4-, and 5-amino-, and 2 : 7- and 2 : 8-diamino-acridines (in the case of 5-aminoacridine, results for pH below 4·8 could not be obtained, as already explained). In general, four bends occur, two of them causing an algebraic increase of slope, and thus related to pK values of the semiquinone, and two in the opposite sense and thus related to pK values of the unreduced substance. Of the latter pair, one occurs at a lower pH value, recorded as pK_1^t in Table II, which corresponds closely with the pK of the unreduced aminoacridine (Table II, last column) determined electrometrically by Albert and Goldacre (*J.*, 1946, 704) for 50% aqueous-alcoholic solutions. The second of these two bends, at pH 12 (pK_2^t in Table II), occurs only for the 2- and 5-amino- and 2 : 7- and 2 : 8-diamino-compounds, for which Albert and Goldacre found only a single pK in each case. It may be significant that these anomalous pK_2^t-bends occur where the supporting electrolyte is changed from buffer solutions to sodium hydroxide solutions, but it has been shown (see below) that

they are not due to the increase in ionic strength associated with this change of supporting electrolyte.

At pH > pK_1' all the aminoacridines are in the free base form T (I). Where a pK_2'-bend occurs, this is true up to pH = pK_2'. At pH < pK_1', down to at least pH 2·5, spectrographic evidence (Craig and Short, *J.*, 1945, 419; Turnbull, *ibid.*, p. 441) indicates that they are in the form T^+ (II), and that addition of a second proton (to substituent amino-group) is at most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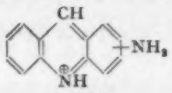
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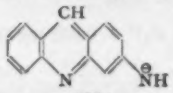
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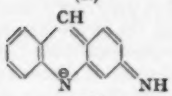
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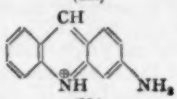
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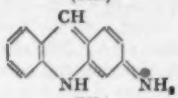
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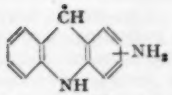
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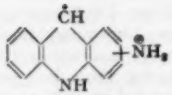
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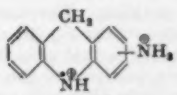

(IX.)

only incomplete at about pH 0. Where a pK_2'-bend occurs, it is difficult to avoid the conclusion that for pH > pK_2' the aminoacridine exists in the form of an anion T^-. The latter might perhaps result from the loss of a proton from the amino-group, giving an ion such as (III), stabilised by resonance with (IV). This view is suggested by the fact that formation of T^- occurs only with 2- or 5-amino-substituted acridines, while strong resonance between structures of the type (V) and (VI), which is precisely similar to that between (III) and (IV), occurs only for 2- and 5-aminoacridine (Albert and Goldacre, *loc. cit.*).

An important feature of the E_1–pH curve, common to all the compounds except 1- and 3-aminoacridine, is the horizontal central section. Here the pH is less than pK_1', so the aminoacridine is mainly present as T^+; also the first reduction step is independent of pH and thus involves no proton uptake. The electrode process may be written

$$T^+ + e \longrightarrow S \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where S denotes the uncharged semiquinone (VII). For a reversible process corresponding to this equation, with standard redox potential $E_1°$, the redox potential in v at 25° is given by

$$E = E_1° + 0{\cdot}059 \log ([T^+]/[S]) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Since two bends associated with the acid constants of the semiquinone occur in the E_1–pH curves for 2-aminoacridine and both diaminoacridines, the semiquinones of these compounds apparently exist at three ionisation levels. Both bends occur at pH lower than where we have already assumed that the semiquinone is in the form S, and thus the remaining two ionisation levels must correspond to successive addition of protons to S, giving ions S^+ and S^{++}. For 4- and 5-aminoacridines, the experimentally accessible pH range did not extend low enough for the second bend and S^{++}-formation to occur. For acridine (*J.*, 1951, 27) there are no bends indicating formation of S^+ and S^{++} down to pH 0. This suggests that S^+ has the structure (VIII), formed by addition of a proton to a substituent amino-group, which is more strongly basic in S than in T^+ because of the additional odd electron in the molecule. Since S^{++}-formation occurs in mono- as well as in di-aminoacridines, it cannot be due to proton addition at a second amino-group; we tentatively assume that the proton is added at the 5-carbon atom, as in (IX).

The concentrations of S, S^+, and S^{++} are inter-related by the following ionisation equilibria :

$$S + H^+ \rightleftharpoons S^+; \quad [S^+] = [S][H^+]/K_2' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$S^+ + H^+ \rightleftharpoons S^{++}; \quad [S^{++}] = [S^+][H^+]/K_1' = [S][H^+]^2/K_1'K_2' \quad . \quad . \quad . \quad (4)$$

Thus the total concentration of semiquinone in all three forms is

$$[Sem] = [S] + [S^+] + [S^{++}] = [S]\{K_1'K_2' + K_1'[H^+] + [H^+]^2\}/K_1'K_2' \quad . \quad (5)$$

Similarly, the total concentration of unreduced material in all three forms is

$$[Ox] = [T^-] + [T] + [T^+] = [T^+]\{K_1^tK_2^t + K_1^t[H^+] + [H^+]^2\}/[H^+]^2 \quad . \quad . \quad (6)$$

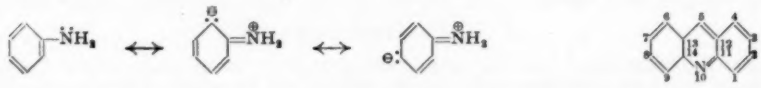
Substituting for $[T^+]$ in terms of [Ox] from equation (6), and for [S] in terms of [Sem] from equation (5), equation (2) becomes, when applied to the half-wave potential (where $E = E_1$ and [Ox] = [Sem]),

$$E_1 = E_1^{\circ\prime} + 0{\cdot}059 \log [H^+]^2\{K_1^sK_2^s + K_1^s[H^+] + [H^+]^2\}/\{K_1^tK_2^t + K_1^t[H^+] + [H^+]^2\} \quad . \quad (7)$$

where $E_1^{\circ\prime} = E_1^{\circ} - 0{\cdot}059 \log K_1^sK_2^s$.

It being assumed that $K_1^s \gg K_2^s \gg K_1^t \gg K_2^t$, it follows from equation (7) that the E_1–pH graph should consist of linear portions separated by bends at pH = pK_1^s, pK_2^s, pK_1^t, and pK_2^t, with slopes −59 mv for pH between pK_1^t and pK_2^t or pK_1^s and pK_2^s, −118 mv below pK_1^s and above pK_2^t, and zero between pK_2^s and pK_1^t. This is in general agreement with the form of the experimental curves of all but the 1- and 3-aminoacridine, although of course no pK_2^t bend occurs in the 4-isomer, and the slopes (Table II) differ from the theoretical values in most cases, probably because the polarographic reduction is thermodynamically irreversible, as with acridine. The discrepancy is least for 2 : 7-diaminoacridine. The central horizontal portions of the E_1–pH curve of 1- and 3-aminoacridine are missing, indicating, according to equation (7), that pK_2^s is not considerably less than pK_1^t, as it is for the other aminoacridines. In fact, analysis of the E_2–pH curves for these two compounds (see below) yields values of pK_2^s (Table II) which are definitely greater than the corresponding pK_1^t values derived from the E_1–pH curves and confirmed by Albert and Goldacre's electrometric data (*loc. cit.*). It being assumed then that for these two compounds $pK_2^s > pK_1^t > pK_1^s$, the E_1–pH graph according to equation (7), the term in K_2^t being omitted, should consist of linear sections separated by bends at pH = pK_2^s, pK_1^t, and pK_1^s, with slopes of −59 mv for pH above pK_2^s or between pK_1^t and pK_1^s, and −118 mv below pK_1^s or between pK_2^s and pK_1^t. For both compounds, the bends actually found (Fig. 4) are not very pronounced, so that, because of the insufficient number of points on the curves, it is difficult to determine whether a pK_1^s bend is present. For the 1-isomer, apart from this difficulty, agreement between theory and experiment (Fig. 4, curve I) is reasonable, although the slopes do not have the theoretical values. For the 3-isomer, however, there is no indication of a pK_2^s bend.

The reason why semiquinone formation enhances the basic strength of a substituent amino-group relative to that of ring nitrogen (*i. e.*, makes $pK_2^s > pK_1^t$) more strongly for the 1- and 3-aminoacridine than for all the other compounds studied, may be stated as follows. For base-weakening resonance of the type :



in the case of all but these two compounds, the unshared electron pair and negative formal charge may reside on the ring nitrogen or on carbon atoms 1, 3, 7, 9, 12, and 13; for 1- and 3-aminoacridines, however, only on carbon atoms 2, 4, 5, 6, 8, 11, and 14; this resonance explains the low pK values for the amino-group of about −1 to +1 found for most of the compounds by Albert and Goldacre (*J.*, 1943, 454), Craig and Short, and Turnbull (*locc. cit.*). Now in the semiquinones, the only ring positions occupiable by the odd electron are 2, 4, 5, 6, 8, 11, and 14; thus the base-weakening resonance is inhibited to a greater extent for 1- and 3-aminoacridines than for the other compounds.

In connexion with a theory relating the antibacterial activity of the aminoacridines to their reduction behaviour (Kaye, *J. Pharm. Pharmacol.*, 1950, **2**, 902), it is significant that the active compounds (i) form apparently highly stable semiquinones, (ii) give E_1–pH curves with a horizontal section, where semiquinone formation involves uptake of an electron only and no proton, and (iii) have this horizontal section covering the biologically important pH region around pH 7. Some inactive compounds comply with (i) and (ii), but only the more active ones comply with (iii) as well. Since (iii) necessitates that $pK_1^t > 7 > pK_2^s$, the correlation between basicity (or pK_1^t) and activity noted by Albert, Rubbo, and Goldacre (*Nature*, 1941, **147**, 332) may be viewed in a new light.

From a consideration of the slopes of the various sections of the E_1–pH curves, we may now

represent the electrode processes for the first reduction step of all but 1-, 3-, and 4-aminoacridine in different pH regions:

$$\text{For pH} > \text{p}K_2^I: \quad T^- + e + 2H^+ \longrightarrow S \quad (8)$$
$$\text{For p}K_2^I > \text{pH} > \text{p}K_1^I: \quad T + e + H^+ \longrightarrow S \quad (9)$$
$$\text{For p}K_1^I > \text{pH} > \text{p}K_2^I: \quad T^+ + e \longrightarrow S \quad (10)$$
$$\text{For p}K_2^I > \text{pH} > \text{p}K_1^I: \quad T^+ + e + H^+ \longrightarrow S^+ \quad (11)$$
$$\text{For pH} < \text{p}K_1^I: \quad T^+ + e + 2H^+ \longrightarrow S^{++} \quad (12)$$

For 4-aminoacridine, with no pK_2^I, equation (8) is inapplicable, equation (9) applies at pH > pK_1^I, and equations (10), (11), and (12) apply unchanged. Similarly, for 1- and (possibly) 3-aminoacridine, equation (9) applies for pH > pK_2^I, equation (12) would apply for pH < pK_1^I if a bend had occurred at pK_1^I, and instead of equations (10) and (11) we now have

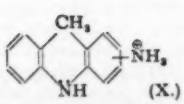
$$\text{For p}K_2^I > \text{pH} > \text{p}K_1^I: \quad T + e + 2H^+ \longrightarrow S^+ \quad (13)$$
$$\text{For p}K_1^I > \text{pH } (> \text{p}K_1^I): \quad T^+ + e + H^+ \longrightarrow S^+ \quad (14)$$

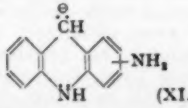
We may now consider the E_2–pH curves (Figs. 4 and 5), which are essentially similar in form for all the compounds (for 5-aminoacridine no results are available for pH < 4·8, as explained previously). Two bends corresponding to pK^I values for the semiquinone appear (only one for the 2-, 4-, and 2 : 7-compound), and two oppositely directed bends, apparently corresponding to pK^r values for the fully reduced product (aminoacridan). The pK^I bends should of course occur at the same pH values as the corresponding bends in the E_1–pH curves. This is seen to be true for the 2- and the 2 : 8-compound (Table II). In the E_1–pH curves of 1- and 3-aminoacridine, pK_1^I bends are missing or doubtful, and the pK_2^I bend is missing for the 3-isomer and in poor agreement with the corresponding E_2–pH bend for the 3-isomer. For the 4- and the 2 : 7-compound the correspondence is only fair, and for 5-aminoacridine E_2–pH data are lacking.

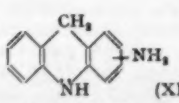
We come now to the two E_2–pH bends apparently related to pK^r values. The one at the lower pH annuls the effect on the slope of two successive pK^I bends, and may thus be regarded as due to two acid constants, pK_1^r and pK_2^r, not greatly different in value. The remaining bend, at about pH 13, is unlikely to indicate that the aminoacridan can ionise off yet another proton, on constitutional grounds. The bend occurs just where sodium hydroxide solutions replace buffers as supporting electrolyte. Since Burstein and Davidson (*Trans. Electrochem. Soc.*, 1941, **63**, 1636) showed that the stability of uncharged semiquinone decreased considerably with rising ionic strength of the solution in the case of certain anthraquinone derivatives, it seemed likely that the increasing ionic strength of the sodium hydroxide solutions at pH 13 and 14 might result in the displacement of the reduction potential of semiquinone to increasingly less negative values. In confirmation of this view, inclusion of N-potassium chloride in 2 : 8-diaminoacridine solutions in 50 alcoholic buffers at pH 10·39 and 12·0 made E_2 about 80 mv less negative. We may thus neglect this bend as an ionic-strength effect. Incidentally, the addition of potassium chloride shifted E_1 also to somewhat less negative values. Hence the anomalous pK_2^I bends on the E_1–pH curves towards more negative potentials with rising pH cannot be due to ionic-strength effects.

From a consideration of the slopes of the various sections of the E_2–pH curves we may write the electrode processes for the second reduction step at various pH regions:

$$\text{For pH} < \text{p}K_1^I: \quad S^{++} + e \longrightarrow R^+ \quad (15)$$
$$\text{For p}K_1^I < \text{pH} < \text{p}K_2^I: \quad S^+ + e + H^+ \longrightarrow R^+ \quad (16)$$
$$\text{For p}K_2^I < \text{pH} < \text{p}K_{1,2}^r: \quad S + e + 2H^+ \longrightarrow R^+ \quad (17)$$
$$\text{For pH} > \text{p}K_{1,2}^r: \quad S + e \longrightarrow R^- \quad (18)$$


(X.)


(XI.)


(XII.)

Here R^+ and R^- denote structures (X) and (XI), respectively; R^-, which probably abstracts a proton from a water molecule immediately after formation, thus changing to the form R

(XII), is similar to the anionic form of reduction product previously postulated for acridine, by analogy with the views of other workers with different substances (*J.*, 1951, 27).

By writing the equation for the electrode potential of a reversible reduction corresponding to equation (18), introducing the dissociation constants $K_1^r = [R][H^+]/[R^+]$, $K_2^r = [R^-][H^+]/[R]$, and proceeding as in the derivation of equation (7), we obtain :

$$E_2 = E_2^{o\prime} + 0{\cdot}059 \log \{K_1^r K_2^r + K_1^r[H^+] + [H^+]^2\}/\{K_1^s K_2^s + K_1^s[H^+] + [H^+]^2\} \quad . \quad (19)$$

It being assumed that $pK_1^s < pK_2^s < pK_1^r \approx pK_2^r$, this equation leads to E_2–pH curves similar to those in Figs. 4 and 5 (especially Fig. 4, curves I and III, and Fig. 5, curve I), except that the slopes of the various portions are multiples of -59 mv. Apart, then, from the discrepancy in slopes (cf. Table II), attributable to thermodynamic irreversibility of the electro-reduction, equation (19) represents satisfactorily the experimental E_2–pH curves for all the compounds.

Although equations (8)—(18) are deducible directly from the E_1–pH and E_2–pH curves, the representation of the latter by means of equations (7) and (19) is open to the possible criticism that these two equations are based on the assumption of reversible equilibria, when at least some of the processes concerned are known to be irreversible. In particular, the existence of pK_2^r appears to be peculiar to the polarographic-electroreduction technique, and it is unlikely to be encountered in electrometric determinations. However, pK_1^r should be real enough and determinable electrometrically. Appropriate comparison data are lacking, apart from the pK values of 4·72 (in 50% alcohol) and 5·2 (in water) given for 3-aminoacridan by Albert and Ritchie (*J.*, 1943, 458) and Albert, Rubbo, Goldacre, Davey, and Stone (*Brit. J. Exp. Path.*, 1945, **26**, 160), respectively, which do not correspond with any bend in the E_1–pH or E_2–pH curve in the present work.

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588. *The Constitution of Mesquite Gum. Part III.* The Structure of the Monomethyl Glucuronic Acid Component.*

By F. Smith.

Prolonged hydrolysis of mesquite gum affords 4-methyl D-glucuronic acid, which has been characterised by means of the α- (VI) and the β-form (V) of 4-methyl methyl-D-glucuronoside amide. These have been converted into the corresponding crystalline amides (IX) and (VIII) of 2 : 3 : 4-trimethyl methyl-D-glucuronoside. Oxidation of the methyl ester (III) of 4-methyl methyl-D-glucuronoside first with sodium periodate and then with bromine, followed by hydrolysis, gives L-*erythro*-2-hydroxy-3-methoxy-succinic acid (X) and glyoxylic acid (XI). Reduction of (III) catalytically or by lithium aluminium hydride yields 4-methyl methyl-D-glucoside (I) and this on hydrolysis gives 4-methyl D-glucose. The last affords crystalline 4-methyl D-glucose phenylosazone identical with an authentic specimen prepared by an unambiguous synthetic route.

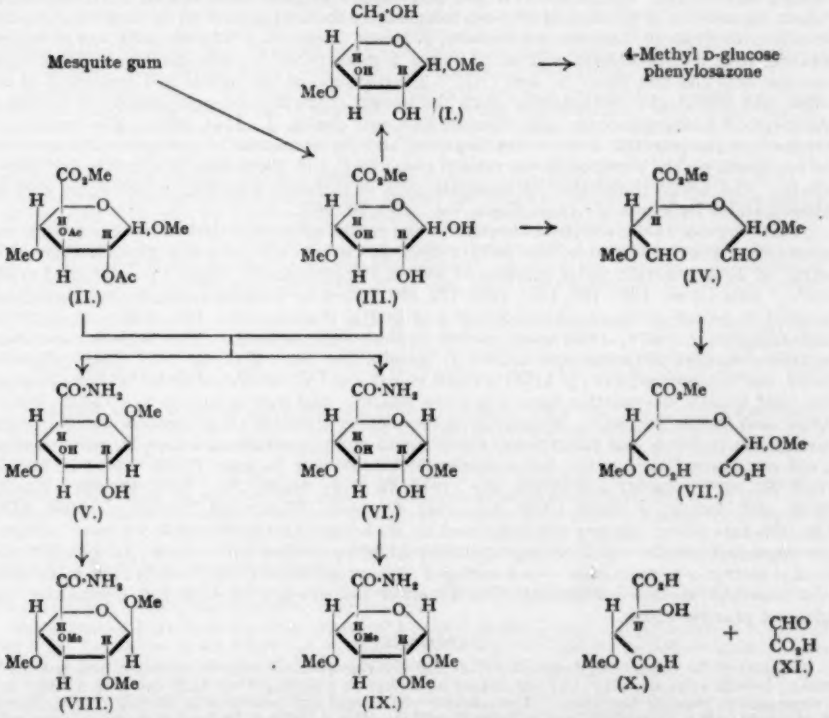
Mesquite gum, exuded by the mesquite tree (*Prosopis Juliflora* D.C. and related species) (Procter, *Amer. J. Pharm.*, 1855, **27**, 14, 223; Morfit, *Amer. J. Sci.*, 1885, **19**, 264), is the neutral salt of a complex acidic polysaccharide (Anderson, Sands, and Sturgis, *Amer. J. Pharm.*, 1925, **97**, 589), which owes the acidic character to the presence of a monomethyl D-glucuronic acid constituent (Anderson and Otis, *J. Amer. Chem. Soc.*, 1930, **52**, 4461). In addition to the latter, mesquite gum contains D-galactose and L-arabinose. Methylation studies (Cunneen and Smith, Part II; * White, *J. Amer. Chem. Soc.*, 1946, **68**, 272; 1947, **69**, 622) and other investigations (White, *ibid.*, 1947, **69**, 715) show that the L-arabinose is present as furanose units while the D-galactose and methyl D-glucuronic acid residues have pyranose structures.

* Part II, *J.*, 1948, 1146.

Mild acid hydrolysis removes the L-arabofuranose residues (Anderson and Sands, *ibid.*, 1926, **48**, 3172) and leaves intact a stable framework or nucleus of degraded mesquitic acid which is composed of the pyranose units of D-galactose and of monomethyl D-glucuronic acid (White, *ibid.*, 1947, **69**, 622; Rao and Smith, unpublished work). More drastic hydrolysis of the degraded mesquitic acid leads to D-galactose and mixed aldobionic acids (Cunneen and Smith, *J.*, 1948, 1141; White, *J. Amer. Chem. Soc.*, 1947, **69**, 2264). The latter are composed of one unit of D-galactose and one of monomethyl D-glucuronic acid for by still further hydrolysis they give rise to D-galactose and a monomethyl D-glucuronic acid (Anderson and Otis, *loc. cit.*).

The present paper deals with the structure of the methyl glucuronic acid residues of mesquite gum. The results confirm those of White (*ibid.*, 1948, **70**, 367) and provide additional proof that the methyl group of the uronic acid residues is at $C_{(4)}$.

When either degraded mesquitic acid or the derived aldobionic acid was subjected to prolonged boiling with methanolic hydrogen chloride simultaneous methanolysis and esterification gave a mixture containing methyl-D-galactoside and the methyl esters of 4-methyl α- and β-methyl-D-glucuronoside (III) and of a methylated aldobiuronoside. The glucuronic and aldobionic acid components could be separated by fractional distillation directly as their ester glycosides or after conversion into the corresponding acetates. Treatment of the methyl ester of the methyl methyl-D-glucuronosides (III) or the acetate (II) with methanolic ammonia yielded a mixture of the amide (VI) of methyl α- and that (V) of the methyl β-methyl-D-glucuronoside. The crystalline forms of these two amides proved to be quite different and their separation by fractional crystallisation was relatively easy.



The methyl ester and acetate of the methylated aldobiuronoside also afforded a crystalline amide, the structure and constitutional significance of which will be dealt with in a later communication.

The structure of the amides (V) and (VI) is based on the following facts. The β-form (V)

was transformed into the α-form (VI) by boiling it with methanolic hydrogen chloride and treating the resulting ester with ammonia. When the amides (V) and (VI) were converted into the corresponding acids and the latter methylated with silver oxide and methyl iodide, the methyl esters of 2 : 3 : 4-trimethyl β- and α-methyl-D-glucuronoside respectively were formed, and these with ammonia yielded the characteristic crystalline amides (VIII) and (IX) respectively of 2 : 3 : 4-trimethyl methyl-D-glucuronoside (Smith, *J.*, 1939, 1724). This proved that the original amides (V) and (VI) were anomers, that they possessed six-membered rings, and that the methyl group occupied position 2, or 3, or 4.

The two forms (VI) and (V) each reacted with one mole of sodium periodate to give dialdehydes (Fleury, Hérissey, and Joly, *J. Pharm. Chim.*, 1934, **20**, 149; Jackson and Hudson, *J. Amer. Chem. Soc.*, 1937, **59**, 994). Similarly the methyl ester (III) consumed one mole of periodate to give the dialdehyde (IV). No formic acid was produced. Since a methyl group at $C_{(3)}$ would render the molecule immune to periodate oxidation, the uptake of one mole indicated that the methyl group was located at either $C_{(2)}$ or $C_{(4)}$. It is of interest that while oxidation of (V) and (VI) proceeded normally with sodium periodate, over-oxidation occurred with periodic acid. Similarly, normal oxidation of the methyl ester took place with either sodium periodate at 5° and at 25° or with periodic acid at 5°, but with the latter extensive over-oxidation took place at 25° (see Huebner *et al.*, *J. Biol. Chem.*, 1945, **159**, 503; Sprinson and Chargaff, *ibid.*, 1946, **164**, 443; Grangaard *et al.*, *Paper Trade J.*, 1942, **115**, Vol. 7, 41; Halsall, Hirst, and Jones, *J.*, 1947, 1427).

Oxidation of the dialdehyde (IV) with bromine in the usual way afforded the corresponding dibasic acid (VII). Compared with the dialdehydes derived from simple sugar glycosides which are cleaved by dilute acid at room temperature the acid proved to be surprisingly stable to acid hydrolysis (cf. Jackson and Hudson, *J. Amer. Chem. Soc.*, 1940, **62**, 958), but prolonged heating with N-hydrochloric acid at 95° gave a mixture of L-*erythro*-2-hydroxy-3-methoxysuccinic acid (X) and glyoxylic acid (XI). Esterification of the former and treatment of the ester with methanolic methylamine gave the known crystalline bismethylamide of L-*erythro*-2-hydroxy-3-methoxysuccinic acid (Heslop, Salt, and Smith, *J.*, 1944, 225). The location of the methyl group in this four-carbon fragment and the formation of glyoxylic acid can only be explained by the presence of the methyl group at $C_{(4)}$ in the methyl glycuronic acid derivatives. The acidic component of mesquite gum is therefore 4-methyl D-glucuronic acid as already stated by White (*J. Amer. Chem. Soc.*, 1948, **70**, 367).

Further proof of the structure assigned to the methyl glucuronic derivatives came from the observation that reduction of the methyl ester of the methyl methyl-D-glucuronoside (III) either by hydrogenation under pressure at 180° in the presence of copper chromite (cf. Levene *et al.*, *J. Biol. Chem.*, 1937, **121**, 155; 1937, **122**, 199, 203) or by treatment with lithium aluminium hydride in tetrahydrofuran (Abdel-Akher and Smith, *Nature*, 1950, **166**, 1037; cf. Lythgoe and Trippett, *J.*, 1950, 1983) gave methyl methyl-D-glucoside (I). The lithium aluminium hydride reduction (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197, 2548; Finholt, Bond, and Schlesinger, *ibid.*, p. 1199) is much superior to hydrogenation under pressure because the yield is high, the reaction takes but a few minutes, and hydrogenolysis is avoided (Abdel-Akher and Smith, *loc. cit.*). Hydrolysis of the methyl glucoside (I) proceeded smoothly with N-sulphuric acid at a rate indicative of the presence of a pyranoside structure, to give 4-methyl D-glucose, characterised as its phenylosazone (McDonald and Jackson, *J. Res. Nat. Bur. Stand.*, 1940, **24**, 181; Schmidt and Müller, *Ber.*, 1943, **76**, 344; Shinle, *Ber.*, 1932, **65**, 315; Knauf, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1447; Munro and Percival, *J.*, 1935, 873). The structure of the osazone was confirmed by its unequivocal synthesis as follows : methyl-α-D-mannopyranoside ⟶ 2 : 3-*iso*propylidene methyl-α-D-mannoside ⟶ 2 : 3-*iso*propylidene 6-trityl methyl-α-D-mannoside ⟶ 4-methyl 2 : 3-*iso*propylidene 6-trityl methyl-α-D-mannoside ⟶ 4-methyl methyl-D-mannoside ⟶ 4-methyl D-mannose ⟶ 4-methyl D-mannose (or -glucose) phenylosazone.

Experimental.

Isolation of the Amide of 4-Methyl Methyl-α- and -β-D-glucuronoside.—(*a*) A solution of mesquite gum (250 g.) in 0·2N-sulphuric acid (1 l.) was heated for 2 days on a boiling water-bath and then dialysed for 2 days against running tap water. The solution was filtered and poured with stirring into methanol (3 volumes). The precipitate was triturated with methanol until it became granular, filtered off, washed with methanol and, while still containing some solvent, boiled for 20 hours with 7—8 parts of 7·5% methyl-alcoholic hydrogen chloride. The crude methylglucuronoside was isolated by neutralisation (silver carbonate), filtration, evaporation *in vacuo* to dryness, and extraction with acetone. Distillation of the crude, pale yellow, thick product gave a viscous liquid (23·4 g.), b. p. 165—170° (bath temp.)/0·05 mm., n_D^{28} 1·4775—1·4790, $[\alpha]_{461}^{28}$ +48° in methanol (*c*, 2·7) (Found : OMe, 32·0%; equiv., 324.

Calc. for $C_9H_{16}O_7$: OMe, 39·4%; equiv., 236). The low methoxyl value and high equivalent weight are caused by the presence of methyl-α- and -β-D-galactosides, both of which are obtained crystalline from the mother-liquors after separation of the amides of the methylated glucuronoside (see below).

Treatment of the crude ester with methyl-alcoholic ammonia gave a crystalline amide (13·5 g.), m. p. 206—212°. Crystallisation from ethanol containing a few drops of water yielded the *amide* of 4-methyl methyl-α-D-glucuronoside as thick plates, m. p. 236°, $[\alpha]_D^{20}$ +150° in water (*c*, 1·0) [Found: C, 43·55; H, 6·9; N, 6·2; OMe, 27·8%; equiv., 224. $C_8H_{15}O_6N$ requires C, 43·5; H, 6·85; N, 6·3; OMe, 28·05%; equiv., 221 (determined by heating the amide with an excess of 0·02N-NaOH on the water-bath in a gentle current of nitrogen and back-titrating the excess of the alkali with 0·02N-H_2SO_4)]. From the mother-liquors the *amide* of 4-methyl methyl-β-D-glucuronoside was obtained as needles, m. p. 232°, $[\alpha]_D^{20}$ −50° in water (*c*, 1·1) (after crystallisation from methanol) (Found: C, 42·9; H, 7·0; N, 6·4; OMe, 28·0%; equiv., 223. $C_8H_{15}O_6N$ requires C, 43·55; H, 6·9; N, 6·3; OMe, 28·05%; equiv., 221).

(*b*) A solution of mesquite gum (200 g.) in 0·5N-sulphuric acid (1 l.) was heated for 12 hours on the boiling-water-bath. Neutralisation (barium hydroxide solution), filtration, evaporation *in vacuo* to a thin syrup, and addition of an excess of methanol gave a precipitate of barium salts. The latter were filtered off and purified by one precipitation from water with methanol. The dried salts were then boiled for 6 hours with 3% methanolic hydrogen chloride. The solution was cooled, neutralised with silver carbonate, filtered, and evaporated to dryness *in vacuo*. The residue was dissolved in methanol (100 c.c.), and ether added cautiously to precipitate inorganic impurity. Removal of the latter on the centrifuge and concentration of the solution *in vacuo* gave a pale yellow liquid which was dissolved in pyridine (50 c.c.) and treated with acetic anhydride (50 c.c., added slowly with shaking). After 10 hours at room temperature and 2 hours at 60° the reaction mixture was poured into ice-water, and the product extracted with chloroform. The combined chloroform extracts were washed successively with N-sulphuric acid, water, and sodium hydrogen carbonate solution, and dried ($MgSO_4$). Removal of the solvent gave a viscous liquid which was distilled giving fraction I (a mixture of the methyl ester of 2 : 3-diacetyl 4-methyl methyl-D-glucuronoside and 2 : 3 : 4 : 6-tetra-acetyl methyl-D-galactoside) (19·9 g.), b. p. 155—165° (bath temp.)/0·03 mm., n_D^{24} 1·4520, $[\alpha]_D^{26}$ +79° in methanol (*c*, 4·5) (Found: OMe, 14·2%; equiv., 90), and fraction II (mainly the methyl ester of a penta-acetyl monomethyl methyl-aldobiuronoside) (2·43 g.), b. p. 260—270°/0·03 mm. (sets to a glassy solid), $[\alpha]_D^{26}$ +64° in methanol (*c*, 2·5) (Found: OMe, 13·3%; equiv., 104. Calc. for $C_{25}H_{36}O_{17}$: OMe, 15·3%; equiv., 101·3).

Treatment of fraction I. This was heated for 2 hours at 60° with an excess of barium hydroxide in 70% methanol in an atmosphere of nitrogen. The solution was neutralised with carbon dioxide, filtered, and evaporated *in vacuo* to dryness. The residue was dissolved in methanol (100 c.c.), and acetone added until precipitation was complete. The precipitate was separated (centrifuge), washed successively with acetone and ether, and dried. The barium salt was boiled for 8 hours with 2% methanolic hydrogen chloride, and the methyl ester of 4-methyl methyl-D-glucuronoside, isolated as described above, was purified by extraction with acetone and finally by distillation (3·7 g.), then having b. p. 165—170°/0·05 mm., n_D^{24} 1·4715—1·4737, $[\alpha]_{5461}^{25}$ +50° in methanol (*c*, 2·7) (Found: OMe, 38·4%; equiv., 240. Calc. for $C_9H_{16}O_7$: OMe, 39·4%; equiv., 236). Treatment of this ester with methyl-alcoholic ammonia gave a good yield of the α- and β-forms of the amide of 4-methyl methyl-D-glucuronoside. Trituration of the mixture of amides with ethanol extracted the β-isomer. Crystallisation of the residue from methanol gave the α-form, m. p. 236°, while the β-isomer (m. p. 232°) was readily isolated from the ethanol extract.

Treatment of fraction II. A solution of fraction II in methanolic ammonia was kept for 10 hours at room temperature and then evaporated *in vacuo* to remove solvent and acetamide. Crystallisation of the residue from aqueous methanol gave the *amide* of a methyl D-glucuronosyl(methyl-D-galactoside), m. p. 267° (decomp.), $[\alpha]_D^{18}$ +25° in water (*c*, 0·6) (Found: OMe, 16·5. $C_{14}H_{25}O_{11}N$ requires OMe, 16·2%).

The barium salt of a methyl aldobionic acid (12·5 g.) [Found: OMe, 7·6; Ba, 15·2 (sulphated ash). Calc. for $C_{12}H_{14}O_{11}(OMe)_2Ba$: OMe, 7·1; Ba, 15·6%] was prepared from mesquite gum (150 g.) by a previous method (Cunneen and Smith, *J.*, 1948, 1141). When boiled for 5 hours with 1·2% methanolic hydrogen chloride, this salt gave an ester which was isolated in the usual way (Found: OMe, 24·9. Calc. for $C_{15}H_{26}O_{12}$: OMe, 23·4%). Direct treatment of this ester with methyl-alcoholic ammonia afforded in good yield the *amide* of the methyl D-glucuronosyl(methyl-D-galactoside), m. p. 267° alone or mixed with the aldobionamide prepared through the acetate (after recrystallisation from aqueous ethanol) (Found: C, 43·1; H, 6·6; N, 3·8; OMe, 16·8. $C_{14}H_{25}O_{11}N$ requires C, 43·8; H, 6·6; N, 3·7; OMe, 16·2%). Small amounts of the α- and β-isomers of the amide of 4-methyl methyl-D-glucuronoside were isolated from the mother-liquors.

The structure and constitutional significance of this amide of methyl D-glucuronosyl(methyl-galactoside) will be dealt with in a later communication.

Determination of the Structure of the Amide of 4-Methyl Methyl-α- and -β-D-glucuronoside.—Methylation: (a) *The α-form of the amide.* A solution of the amide of 4-methyl methyl-α-D-glucuronoside (0·47 g.) in water (25 c.c.) was heated for 3—4 hours at 60—70° with 0·1025N-sodium hydroxide (30 c.c.) in a stream of nitrogen (bubbled through the solution), until all the ammonia was expelled. The solution was neutralized with 0·107N-sulphuric acid (9·2 c.c. required which corresponds to an equiv. wt. of 224 for the amide. Calc.: equiv., 221). More acid (18·8 c.c.; 0·107N.) was added to liberate the organic acid which was isolated by evaporation to dryness *in vacuo* and extraction with ethanol. Two treatments of the 4-methyl methylglucuronoside thus isolated with Purdie's reagents gave the *methyl* ester of 2 : 3 : 4-trimethyl methyl-α-D-glucuronoside (0·3 g.), b. p. (bath-temp.) 100°/0·1 mm., n_D^{27} 1·4475, $[\alpha]_D^{26}$ +156° in methanol (*c*, 2·0) (Found: OMe, 58·0. $C_{11}H_{20}O_7$ requires OMe, 58·7%). Treatment of this ester with methanolic ammonia gave the corresponding *amide* of 2 : 3 : 4-trimethyl

methyl-α-D-glucuronoside, m. p. 188—189°, $[\alpha]_D^{25}$ +149° in water (*c*, 0·25) (after recrystallisation from ethanol–ether–light petroleum) (Found : C, 48·1; H, 7·9; N, 6·0; OMe, 49·4. $C_{16}H_{31}O_9N$ requires C, 48·2; H, 7·7; N, 5·6; OMe, 49·8%). A specimen (m. p. 183°; $[\alpha]_D^{20}$ +138° in water) of this amide prepared from a mixture of the α- and the β-form of the methyl ester of 2 : 3 : 4-trimethyl methyl-D-glucuronoside was evidently not pure (Smith, *J.*, 1939, 1724).

(b) *The β-form of the amide.* The amide of 4-methyl methyl-β-D-glucuronoside (109·5 mg.) was treated with dilute aqueous sodium hydroxide as for the α-isomer (4·6 c.c. of 0·107N. required, corresponding to equiv., 223). The acid was isolated and methylated as above to give the methyl ester of 2 : 3 : 4-trimethyl methyl-β-D-glucuronoside (140 mg.), b. p. (bath-temp.) 120°/0·15 mm., n_D^{27} 1·4520, which afforded the amide of 2 : 3 : 4-trimethyl methyl-β-D-glucuronoside, m. p. and mixed m. p. 190° (after recrystallisation from ethyl acetate or dioxan–ether) (cf. Smith, *loc. cit.*). A mixture of this fully methylated β-isomer with an equal amount of the fully methylated α-form obtained as in (a) had m. p. 158° (cf. Hirst and Jones, *J.*, 1938, 1174; Lythgoe and Trippett, *loc. cit.*).

Oxidation with sodium periodate : (a) *The α-form of the amide.* A solution of the amide of 4-methyl methyl-α-D-glucuronoside (55·2 mg.) in water (5 c.c.) was treated at room temperature with sodium metaperiodate (10 c.c.; 0·27N.). After 2—3 hours (rotation constant, $[\alpha]_D^{20}$ −16°), 1·06 moles of periodate had been consumed per mole of amide. No formic acid was formed. When the reaction mixture was kept in the dark for as long as 70 hours the rotation remained constant and no further uptake of periodate occurred.

(b) *The β-form of the amide.* When the amide of 4-methyl methyl-β-D-glucuronoside (42·9 mg.) was treated with 0·083N-sodium metaperiodate (50 c.c.), the periodate consumption per mole of amide was noted as follows : 0·2 (after 15 mins.); 0·28 (51 mins.); 0·8 (147 mins.); 1·05 (470 mins.); 1·05 moles (24 hours). No acidity was produced in the solution.

Oxidation with periodic acid : (a) *The α-form of the amide.* When the amide of 4-methyl methyl-α-D-glucuronoside (52·6 mg.) in 0·08N-periodic acid (45 c.c.) was kept at room temperature in daylight, oxidation was rapid and overoxidation occurred thus : 0·50 mole of HIO_4 per mole of amide after 6 mins.; 0·85 (after 30 mins.); 1·13 (60 mins.); 1·35 (120 mins.); 1·45 (180 mins.).

When carried out in the dark the oxidation proceeded more slowly but overoxidation was again noticeable and there was no arrest at the stage corresponding to the consumption of 1 mole of acid per mole of amide : 0·2 mole (after 15 mins.); 0·38 (30 mins.); 0·67 (60 mins.); 0·82 (90 mins.); 0·92 (120 mins.); 0·97 (150 mins.); 1·0 (180 mins.); 1·05 (240 mins.); 1·1 (300 mins.); 1·15 (360 mins.); 1·18 (420 mins.).

(b) *The β-form of the amide.* The results were similar to those with the α-isomer. *Interconversion of the α- and the β-forms of the amide of 4-methyl methyl-D-glucuronoside.* The amide of 4-methyl methyl-β-D-glucuronoside (80 mg.) was boiled for 6 hours with 1·5% methyl-alcoholic hydrogen chloride (3 c.c.). The solution was cooled, neutralised with ethereal diazomethane, filtered to remove a small amount of flocculent precipitate, and evaporated *in vacuo* to dryness. Treatment of the syrupy product with methanolic ammonia in the usual way gave a crystalline amide. Slow crystallisation of this from methanol afforded two distinct types of crystal, needles and plates in about equal amounts. On washing by decantation with cold (0—5°) methanol the needles dissolved while the plates of the α-form of the amide remained [m. p. and mixed m. p. 236° (from ethanol)]. Evaporation of the methanolic washings gave the original β-form, m. p. and mixed m. p. 232° (from methanol).

Oxidation of the amide of 4-methyl methyl-D-glucuronoside with sodium periodate and identification of 2-hydroxy-3-methoxy-L-erythrosuccinic acid. A solution of the amide of 4-methyl methyl-α- and -β-D-glucuronoside (3·0 g.) in 0·27N-sodium periodate (125 c.c.) was kept at 25° until the rotation became constant : $[\alpha]_{5461}^{25}$ +115° (after 3 mins.); +92° (5 mins.); +65° (8 mins.); +35° (11 mins.); +4·6° (17 mins.); −21° (23 mins.); −42·5° (34 mins.); −60° (52 mins.); −72° (103 mins.); −72·5° (143 mins.); −60° (356 mins.); −39° (1090 mins.); −35° (1500 mins.); −31·5° (1850 mins.); −28° (3000 mins.), constant for 16 hours. Examination of the solution after 2850 mins. showed that 0·98 mole of periodate had been consumed per mole of amide. The reaction mixture was treated with dilute barium acetate solution until precipitation was complete. Removal of the precipitate (centrifuge) and the solvent (evaporation *in vacuo* at 35—40°) gave a colourless residue which restored the colour to Schiff's reagent but did not reduce boiling Fehling's solution.

A solution of the residue obtained above in water (35 c.c.) was treated for 2 days in the dark at 25° with bromine (1 c.c.) in the presence of barium carbonate (3 g.). The excess of the bromine was removed by aeration and the solution concentrated under diminished pressure. The solution (Schiff's test negative) was treated with hydrochloric acid (30 c.c.; *d* 1·2) and heated for 16 hours on the boiling-water-bath until the rotation became constant ($[\alpha]_{5461}^{20}$ +37·5°). Compared with the dialdehyde prepared from sugar glycosides this dialdehyde formed from 4-methyl methylglucuronoside thus proved to be surprisingly stable. The solution now restored the colour to Schiff's reagent and the test for glyoxylic acid (tryptophan–H_2SO_4) was positive. The solution was neutralised with N-sodium hydroxide and evaporated *in vacuo* to dryness. This residue, containing the salt of 2-hydroxy-3-methoxy-L-*erythro*-succinic acid, was boiled for 6 hours with 3·0% methanolic hydrogen chloride (200 c.c.). Ether (200 c.c.) was added to precipitate inorganic salts. The solution was evaporated *in vacuo* to half-volume, neutralised with silver carbonate, filtered, and evaporated *in vacuo* to dryness. The syrupy residue was further purified by dissolution in acetone (50 c.c.) and addition of ether (175 c.c.). Filtration and removal of solvent afforded a mobile liquid which on distillation gave methyl 2-hydroxy-3-methoxy-L-*erythro*succinate (1·1 g.), b. p. (bath-temp.) 120°/0·5 mm., n_D^{20} 1·4415, $[\alpha]_D^{25}$ +41° in methanol (*c*, 2·0) (Found : OMe, 49·0%; equiv., 107. Calc. for $C_7H_{12}O_6$: OMe, 48·5%; equiv., 96). $[\alpha]_D^{18}$ −43° in methanol, n_D^{17} 1·4440, has been recorded for this ester (Haworth, Heslop, Salt, and Smith, *J.*, 1944, 217).

Treatment of the ester with methanolic methylamine in the usual way gave a good yield of the

crystalline bismethylamide, m. p. 137°, $[\alpha]_D^{20}$ −10·5° in water (*c*, 1·5) (Found: C, 44·0; H, 7·3; OMe, 16·7. Calc. for $C_7H_{14}O_4N_2$: C, 44·2; H, 7·4; OMe, 16·3%). Mixed with the enantiomorph (m. p. 137°; $[\alpha]_D^{18}$ +10·5° in water; Heslop, Salt, and Smith, *J.*, 1944, 225) it had m. p. 122—125° (cf. White, *J. Amer. Chem. Soc.*, 1948, **70**, 367).

Methyl Ester of 4-Methyl Methyl-α-D-glucuronoside.—A solution of the amide of 4-methyl methyl-α-D-glucuronoside (1·06 g.) in 0·1N-sodium hydroxide (80 c.c.) was heated for 5 hours at 60—70° in nitrogen, bubbled through the liquid until no more ammonia was evolved. The solution was treated with 0·1N-sulphuric acid (79 c.c.) and evaporated to dryness *in vacuo*. Extraction with acetone gave 4-methyl methyl-α-D-glucuronoside as a colourless viscous liquid. Attempted lactonisation of a small portion (0·1 g.) of this product by distillation in a high vacuum resulted in decomposition: a small amount of an unidentified crystalline sublimate was produced (m. p. 118°) which was acidic in character and reduced Fehling's solution actively; this may be related to the unsaturated derivatives of glucosaccharolactone (Heslop and Smith, *J.*, 1944, 637).

Treatment of the main portion of the 4-methyl methyl-α-D-glucuronoside with ethereal diazomethane afforded the corresponding *methyl* ester (0·8 g.), b. p. (bath-temp.) 160—170°/0·05 mm., n_D^{20} 1·4720, $[\alpha]_D^{20}$ +128° in water (*c*, 1·0) (Found: OMe, 39·7. $C_8H_{16}O_7$ requires OMe, 39·4%).

Oxidation: (a) *With sodium periodate.* When the methyl ester (58·2 mg.) was allowed to react with 0·08N-sodium periodate at room temperature in the dark the oxidation proceeded according to the following results: 0·06 mole of periodate (after 10 mins.); 0·55 (65 mins.); 0·78 (110 mins.); 1·01 (270 mins.). No further consumption of periodate was observed after 34 hours. A second experiment showed that 1 mole of the ester consumed 0·99 mole of sodium periodate under the same conditions.

(b) *With periodic acid.* At room temperature and in the dark the consumption of periodate (0·08N.) in moles per mole of ester was: 0·93 (50 mins.); 1·38 (290 mins.); 1·57 (450 mins.); 1·75 (2 days). There was thus overoxidation.

At 0° in the dark and with 0·01N-periodic acid the reaction was slower and reached a constant value corresponding to the consumption of 1 mole of periodate per mole of ester: 0·08 (38 mins.); 0·25 (5·5 hrs.); 0·37 (9·7 hrs.); 0·55 (21·5 hrs.); 0·82 (45·5 hrs.); 0·94 (69·5 hrs.); 1·05 (95·3 hrs.), constant for 70 hours.

In a second experiment with 0·01N-acid, 1·05 moles of periodate were consumed per mole of ester in 90 hours (constant for a further 140 hours). When the temperature of this reaction mixture was allowed to rise to 25° (in the dark) overoxidation occurred: 1·23 moles of periodate consumed per mole of ester (after 50·5 hrs.); 1·31 moles (72 hrs.); 1·4 (120 hrs.); 1·69 (174 hrs.).

It is apparent that at room temperature it is better to use sodium periodate than periodic acid, while at 0° both periodic acid and its sodium salt may be used.

Reduction of the Methyl Ester of 4-Methyl Methyl-D-glucuronoside to 4-Methyl Methyl-D-glucoside.—(a) *By hydrogenation.* A solution of the methyl ester of 4-methyl methyl-α- and -β-D-glucuronoside (2·5 g.) in methanol (140 c.c.) was hydrogenated at 175°/4000 lbs. per sq. in. in the presence of copper chromite (2·5 g.). Filtration and removal of solvent gave a colourless viscous liquid (2·3 g.), $[\alpha]_D^{28}$ +78·5° in water (*c*, 2·5) (Found: OMe, 26·2. Calc. for $C_8H_{16}O_6$: OMe, 29·8%). No ester group could be detected by hydrolysis at 50—60°, thus showing hydrogenation was complete. The low methoxyl value is probably due to the fact that some hydrogenolysis occurred.

When a solution of the above 4-methyl methyl-α- and -β-D-glucoside (2·1 g.) in N-sulphuric acid (25 c.c.) was heated on the water-bath for 24 hours the rotation changed from $[\alpha]_D^{28}$ +78° (initial value) to +47° (final). Neutralisation [$Ba(OH)_2$ and then $BaCO_3$], followed by removal of the barium sulphate and the solvent gave 4-methyl D-glucose as a yellow viscous liquid (2·0 g.), $[\alpha]_D^{20}$ +13·5° in water (*c*, 5·0) (Found: OMe, 15·5. Calc. for $C_7H_{14}O_6$: OMe, 16·0%). The low rotation (+47°, equilibrium value of hydrolysis solution) of this 4-methyl D-glucose as compared with that (+59°) shown by the 4-methyl D-glucose obtained from 4-methyl methyl-α-D-glucoside prepared from the 4-methyl methyl-α-D-glucuronoside by reduction with lithium aluminium hydride (see below) is probably due to the presence of some 4-methyl sorbitol arising from hydrogenolysis [Munro and Percival (*loc. cit.*) give $[\alpha]_D$ +53° in water for 4-methyl D-glucose]. The discrepancy between the specific rotation (+47°) of the hydrolysis mixture and that (+13·5°) shown by the syrupy 4-methyl D-glucose after isolation would appear to indicate that the barium hydroxide effected a partial Lobry du Bruyn transformation.

The 4-methyl D-glucose (0·28 g.) in water (5 c.c.) containing acetic acid (0·5 c.c.) was heated for 2 hours at 80—85° with phenylhydrazine (0·8 c.c.). The reaction mixture was poured into water and the precipitate separated on the centrifuge. Recrystallisation from 20% aqueous acetone gave 4-methyl D-glucose phenylosazone as pale yellow needles, m. p. 158°, $[\alpha]_D^{25}$ −32·5° initial value in ethanol (*c*, 0·6), changing in 20 hours to −1·5° (approx.) (Found: C, 61·4; H, 6·6; N, 15·2; OMe, 8·8. Calc. for $C_{19}H_{24}O_4N_4$: C, 61·3; H, 6·5; N, 15·1; OMe, 8·3%).

(b) *With lithium aluminium hydride.* A solution of the methyl ester of 4-methyl methyl-α-D-glucuronoside (200 mg.) in dry tetrahydrofuran (10 c.c.) was slowly added with stirring to a solution of lithium aluminium hydride (300 mg.) in dry tetrahydrofuran (20 c.c.). After 15 minutes an excess of water was added to the reaction mixture which was filtered, and the residue was washed. Evaporation of the filtrate under reduced pressure gave a syrup (160 mg.) which was purified by dissolution in ethanol (1 c.c.) and addition of ether (8 c.c.). Filtration to remove a small amount of precipitate and concentration to dryness *in vacuo* gave *4-methyl methyl-α-D-glucoside* as a colourless, neutral, non-reducing liquid which showed n_D^{27} 1·4790, $[\alpha]_D^{27}$ +133° in water (*c*, 3·5). It did not react with warm 0·01N-sodium hydroxide. After being boiled with 1·5N-sulphuric acid for a few minutes the solution reduced boiling Fehling' solution (Found: OMe, 29·4. $C_8H_{16}O_6$ requires OMe, 29·8%).

When a solution of the 4-methyl methyl-D-glucoside (93 mg.) in N-sulphuric acid (5 c.c.) was heated on the boiling-water-bath the rotation changed in 15 hours from $[\alpha]_D^{25}$ +135° (initial value) to $[\alpha]_D^{25}$ +59°

(constant). The solution was neutralised by passing it through a column of "Duolite" A_4 anion-exchange resin and evaporated *in vacuo* to dryness. The 4-methyl glucose thus obtained (70 mg.) showed $[\alpha]_D^{25}$ +80° in methanol (*c*, 1·3) (Found: OMe, 17·0. Calc. for $C_7H_{14}O_6$: OMe, 16·0%).

The 4-methyl D-glucose (50 mg.) was warmed in water (2·5 c.c.) containing acetic acid (0·25 c.c.) for 2 hours at 80° with phenylhydrazine (0·2 c.c.). On cooling, 4-methyl D-glucose phenylosazone readily crystallised as long needles, m. p. 158—159°, $[\alpha]_D^{26}$ −31°, changing to −2° (equilibrium value) in ethanol (*c*, 0·5) (after crystallisation from 30% aqueous acetone) (Found: N, 14·7. Calc. for $C_{19}H_{24}O_4N_4$: N, 15·1%).

Synthesis of 4-*Methyl* D-*Glucose Phenylosazone.*—A solution of 2 : 3-*iso*propylidene methyl-α-D-mannoside (1·0 g.), prepared by the method of Ault, Haworth, and Hirst (*J.*, 1935, 317), in dry pyridine (10 c.c.) was treated with triphenylmethyl chloride (1·1 g., 1 mol.). After 1 day at room temperature the reaction mixture was warmed for 1 hour at 55—60°, cooled, and poured into water. The syrupy product was triturated, washed by decantation with water, and dissolved in benzene (50 c.c.), and the solution washed successively with N-sulphuric acid (four times), dilute sodium hydrogen carbonate solution, and water. After being dried ($CaCl_2$), evaporation to dryness *in vacuo* gave 2 : 3-iso*propylidene* 6-*trityl methyl*-α-D-*mannoside* as a colourless glassy solid (yield, almost quantitative), $[\alpha]_D^{27}$ +11° in ethanol (*c*, 1·1) (Found: OMe, 6·5. $C_{29}H_{32}O_6$ requires OMe, 6·5%).

Two treatments of the above compound with silver oxide and methyl iodide in the usual way furnished 4-*methyl* 2 : 3-iso*propylidene* 6-*trityl methyl*-α-D-*mannoside* as a viscous pale yellow liquid (1·9 g.), $[\alpha]_D^{27}$ +16·5° in methanol (*c*, 3·3) (Found: OMe, 12·95. $C_{29}H_{34}O_6$ requires OMe, 12·65%).

This product (1·8 g.) was boiled for 8 hours with 3·3% methanolic hydrogen chloride (20 c.c.). Neutralisation (Ag_2CO_3) of the solution followed by removal of solvent gave a residue which was shaken with ether (50 c.c.)–water (20 c.c.). Separation of the aqueous layer, followed by its evaporation to dryness *in vacuo*, yielded syrupy 4-methyl methyl-D-mannoside (0·63 g.), $[\alpha]_D^{27}$ +60·5° in water (*c*, 1·8) (Found: OMe, 31·0. Calc. for $C_8H_{16}O_6$: OMe, 29·8%).

When a solution of the 4-methyl methyl-D-mannoside (0·6 g.) in N-sulphuric acid (25 c.c.) was heated for 12 hours on the boiling-water-bath the rotation reached a constant value of $[\alpha]_D^{25}$ +17°. Neutralisation with N-sodium hydroxide, followed by evaporation *in vacuo* to dryness and extraction with ethanol, gave 4-methyl D-mannose as a viscous syrup (0·53 g.), $[\alpha]_D^{25}$ −2° (approx.) in water (*c*, 3·0).

A portion (0·1 g.) of the 4-methyl D-mannose was treated with phenylhydrazine in dilute acetic acid as described above. Crystallisation of the crude product from aqueous acetone yielded 4-methyl D-mannose phenylosazone in the form of long yellow needles, m. p. 157°. There was no depression of the m. p. when mixed with the two samples of 4-methyl D-glucose phenylosazone described above. The 4-methyl D-mannose phenylosazone showed $[\alpha]_D^{25}$ −34°, initial value in ethanol (*c*, 2·5), changing in 24 hours to −1·5° (approx.) (equilibrium value) (cf. Schmidt and Müller, *loc. cit.*) (Found: C, 61·4; H, 6·6; OMe, 8·3. Calc. for $C_{19}H_{24}O_4N_4$: C, 61·3; H, 6·5; OMe, 8·3%).

The author thanks Mr. J. A. Kent, of the University of Birmingham, for assistance in the preparation of 4-methyl methyl-D-glucuronoside.

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589. *Researches on Acetylenic Compounds. Part XXXII.* Dehydration of Acetylphenyl- and Vinylacetylenyl-alcohols derived from* cyclo*Hexanone, and the Hydration of the Resultant Hydrocarbons.*

By J. C. HAMLET, H. B. HENBEST, and E. R. H. JONES.

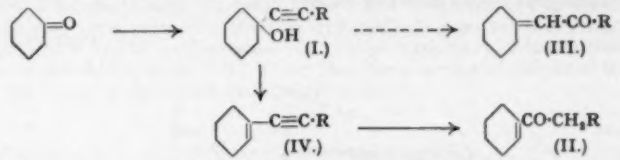
Tertiary alcohols obtained by condensing *cyclo*hexanone with monosubstituted acetylenes or vinylacetylenes can be dehydrated with phosphorus oxychloride in pyridine to compounds containing the conjugated systems C:C·C:C and C:C·C:C·C:C respectively in excellent yields. 1-Ethynyl*cyclo*hexanol itself gives 1-ethynyl*cyclo*hexene in 80% yield, representing a considerable improvement over previous procedures.

The ethynyl*cyclo*hexenes are readily hydrated to yield αβ-unsaturated ketones, whereas vinylogues are hydrated with greater difficulty and then tend to afford cyclised products (derivatives of 4 : 5 : 6 : 7-tetrahydroindan-1-one). Some experiments with alcohols prepared from 2 : 2-dimethyl- and 2 : 2 : 6-trimethyl-*cyclo*hexanone are also described.

MUCH evidence (cf. Chanley, *J. Amer. Chem. Soc.*, 1948, **70**, 244) has indicated that the formic acid-induced isomerisation of ethynylcarbinols leads almost entirely to αβ-unsaturated methyl

* Part XXXI, *J.*, 1951, 766.

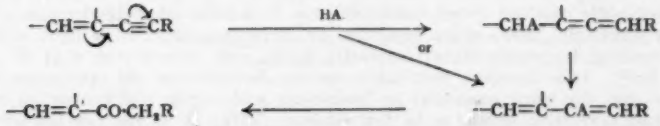
ketones, and that only minor amounts of αβ-unsaturated aldehydes (as first suggested by Rupe, *Helv. Chim. Acta*, 1926, **9**, 672) are produced. Furthermore, Hennion, Davis, and Maloney (*J. Amer. Chem. Soc.*, 1949, **71**, 2813) have shown that this " isomerisation " reaction proceeds by dehydration, followed by hydration of the conjugated unsaturated hydrocarbon.



No examples of the isomerisation of alcohols prepared from monosubstituted acetylenes have as yet been described. In the present work, this extension was studied first with the alcohol (I; R = Bu^n), prepared from *cyclo*hexanone and hex-1-ynylmagnesium bromide in 80% yield. Heating this alcohol with formic acid for ten minutes gave a mixture of the hydrocarbon (IV; R = Bu^n) and the unsaturated ketone (II; R = Bu^n). Longer periods of reaction (45 minutes) increased the yield of the ketone at the expense of the hydrocarbon, indicating that the latter was the intermediate, and this was confirmed by heating the hydrocarbon (see below) with formic acid, the ketone being produced in good yield. The ketone was also formed from the unsaturated hydrocarbon by the boron trifluoride–methanol hydration method of Hennion and Zoss (*J. Amer. Chem. Soc.*, 1941, **63**, 1151). The structure of this ketone was confirmed by ozonolysis, *n*-hexanoic acid being isolated in 65% yield, and also by synthesis from *cyclo*hexene and *n*-hexanoyl chloride (cf. Nightingale, Milberger, and Tomisek, *J. Org. Chem.*, 1948, **13**, 357).

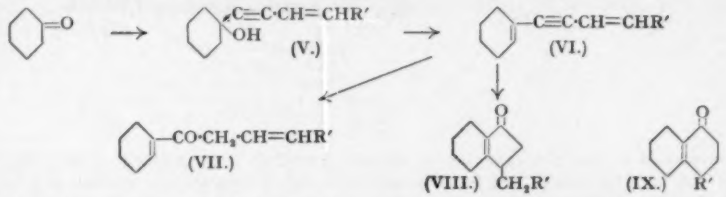
Dehydration of the alcohol (I; R = Bu^n) to the ethynyl*cyclo*hexene was first accomplished by conversion into the tertiary chloro-compound by means of phosphorus pentachloride, followed by dehydrochlorination with pyridine. Phosphorus oxychloride in pyridine was then found to effect the dehydration in one operation in 75% yield. This method has been found to be of general applicability for conversion of alcohols of formula (I) into unsaturated hydrocarbons. 1-Ethynyl*cyclo*hexene can thus be obtained from 1-ethynyl*cyclo*hexanol in 80% yield, by a process far more convenient than those described previously (cf. Eglinton and Whiting, *J.*, 1950, 3650, where previous references are given).

In the formic acid isomerisation described above, it was noteworthy that only one ketone was apparently formed, as judged by careful chromatography of the total 2 : 4-dinitrophenylhydrazone. This observation signifies that the dehydration takes place much more rapidly than the alternative 1 : 3-anionotropic shift of the hydroxyl group, which would lead to the isomeric ketone (III; R = Bu^n) or its βγ-isomer. The production of the small amounts of αβ-unsaturated aldehydes from unsubstituted ethynyl-alcohols (Chanley, *loc. cit.*) must involve this type of anionotropic rearrangement. Formation of the ketone (II; R = Bu^n) is in accord with the direction of polarisation in vinylacetylenic systems as shown, for instance, by the addition of hydrogen halides (Carothers and Berchet, *J. Amer. Chem. Soc.*, 1933, **55**, 2807):



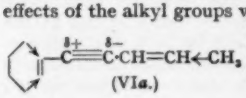
The formation, dehydration, and subsequent hydration of vinylacetylenic alcohols derived from *cyclo*hexanone were next investigated. Nazarov and Pinkina (*Chem. Abs.*, 1948, **42**, 7732) have recently dehydrated (with 50% sulphuric acid) the alcohol (V; R′ = H) to obtain the hydrocarbon (VI; R′ = H). Hydration of the latter with mercuric sulphate in methanol containing a little sulphuric acid yielded a ketone, believed to be (VII; R′ = H), which was cyclised by heating it with a mixture of formic and phosphoric acids to give an isomeric ketone, formulated as (VIII; R′ = H). Repetition of their experiments gave essentially similar results, except that it seems probable that the cyclisation actually occurs during the hydration stage, and that the subsequent treatment with acid effects no appreciable change. This conclusion is supported by the similarity of the physical constants

of the two materials as reported by Nazarov and Pinkina, and confirmed in the present work, and also by the fact that they both afford the same 2 : 4-dinitrophenylhydrazone. No proof of structure was advanced by the Russian workers for their products; it is believed that the cyclised compound does in fact contain a five-membered ring, as suggested by Nazarov and Pinkina, for reasons that will be discussed later.



The homologous alcohol (V; R′ = Me) was prepared from the Grignard derivative of pent-2-en-4-yne (Eglinton and Whiting, *loc. cit.*) in 70% yield, and was dehydrated by phosphorus oxychloride to the corresponding hydrocarbon (VI; R′ = Me) in 85% yield. Heating the alcohol with formic acid under the normal isomerisation conditions gave no ketonic products, but, instead, a good yield of hydrocarbon was obtained. Longer periods of reaction, or heating the hydrocarbon itself with formic acid, gave no appreciable amounts of ketone. Hydration of the hydrocarbon was then attempted by Nazarov and Pinkina's procedure, but here a striking difference from the lower homologue was observed, for little reaction took place, the greater part of the hydrocarbon being recovered unchanged.

The difficulties encountered in hydrating this ·C:C·C:C·C:C· system, compared with the ease with which the mild hydrating reagent, formic acid, reacts with the ·C:C·C:C· compound, can be attributed to the relatively great "electronic symmetry" of the triple bond (or the ·C:C·C:C·C:C· system), leading to only a weak polarisation in any one direction. The marked difference in reactivity of the triple bond in the two compounds (VI; R′ = H and Me) towards mercuric-catalysed hydration may then be explained by the difference in the degree of alkyl substitution of the double bonds on either side of the triple bond, the former with two (ring-)alkyl groups on one double bond and none on the other being less symmetrical than the latter with two and one alkyl groups respectively. In these compounds, the inductive effects of the alkyl groups will also control the direction of hydration (cf. VI*a*). It would thus be expected that in the two compounds under discussion the resultant ketone group will be situated nearer to the more alkylated double bond. That the hydration does, in fact, proceed in the direction suggested will be apparent from the ensuing discussion. It may be noted that the direction of hydration of unsymmetrically substituted triple bonds should provide a useful method of comparing the electronic effects of various types of substituents (cf., Robinson and Robinson, *J.*, 1926, 2204).



(VI*a*.)

The action of the more powerful hydration reagent, boron trifluoride–mercuric oxide in methanol, on the hydrocarbon (VI; R′ = Me) was next examined. From the first experiment a 30% yield of a semicarbazone was obtained. This, however, was a mixture, for, although not easily resolved by crystallisation, two 2 : 4-dinitrophenylhydrazones (m. p. 123° and 193° respectively), were easily separated by chromatography. The light absorption of the lower-melting, less easily eluted derivative agrees very closely with that of the ketone (II; R = Bu^n). It is therefore believed to be the derivative of the open-chain compound (VII; R′ = Me), this being confirmed by phosphoric acid–formic acid cyclisation to give the higher-melting derivative, shown to be derived from (VIII; R′ = Me) (see below).

Modification of this hydration procedure led to a 40% yield of a homogeneous semicarbazone, convertible into the higher-melting 2 : 4-dinitrophenylhydrazone and by hydrolysis into a ketone which, although αβ-unsaturated, resisted hydrogenation in acetic acid with a palladium catalyst and also mild ozonolysis. These facts, together with the ease of elution of the 2 : 4-dinitrophenylhydrazone and the high melting points of the derivatives, suggested that cyclisation had occurred to give most probably (VIII; R′ = Me) or (IX; R′ = Me). Analogously, Nazarov and Pinkina's cyclised compound would be (VIII; R′ = H) or (IX; R′ = H). The presence of a *cyclo*pentenone ring in both ketones was indicated by the carbonyl stretching frequency in the infra-red absorption spectrum (determined by the late Dr. H. P. Koch), and by the ultra-violet absorption spectrum of the ketone and its semicarbazone, characteristic of

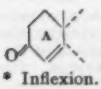
*cyclo*pentenones (cf. Gillam and West, *J.*, 1942, 486). Further there was close agreement (see Table) of the light absorption of the semicarbazones and 2 : 4-dinitrophenylhydrazones of (VIII; R′ = H and Me) with those of the corresponding derivatives of the parent ketone of the series (VIII; CH_2R' replaced by H), these derivatives being kindly supplied by Dr. D. W. Mathieson (cf. Mathieson, *J.*, 1951, 177). Since hydration of the triple bond in the diolefinic acetylenes must precede cyclisation, the cyclic ketones are presumably formed by way of an open-chain ketone, but, whatever the precise mechanism of the cyclisation reaction, the formation of products such as (VIII) shows that the direction of the initial hydration is in accord with the simple electronic effects referred to above.

	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$		$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$
Compounds containing C=C—C≡C.					
(IV; R = H)	2235	10,500	(V; R′ = Me)	2260	14,500
(IV; R = Bu^n)	2270	10,500		2340 *	12,000
	2300 *	10,000	2 : 2-Dimethyl derivative of (V; R′ = Me)	2275	15,500
2-Hex-1′-ynyl-3 : 3-dimethyl-*cyclo*hexene	2280	12,500	(V; R′ = CH_2·OH)	2260	12,500
(V; R′ = H)	2240	13,500	2 : 2-Dimethyl derivative of (V; R′ = CH_2·OH)	2290	16,000
	2340	11,500			
Compounds containing C=C—C≡C—C=CH_2.					
(VI; R′ = H)	2610	14,500	(VI; R′ = Me)	2640	13,000
(VI; R′ = CH_2·OH)	2645	13,000	2 : 2-Dimethyl derivative of (VI; R′ = Me)	2700	13,000

cyclo*Hex*-1-*enyl ketones*, C_6H_9·COR.

	Ketone		Semicarbazone		2 : 4-Dinitrophenylhydrazone †	
R	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$ (Å)	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$
Me	2320	12,500	2605	24,500	2550	16,500
					3850	27,000
n-C_6H_{11}	2340	12,000	2615	23,500	2570	16,500
					3870	28,000
CH_2·CH:CHMe	—	—	—	—	2570	17,500
					3870	28,500

Cyclised compounds, etc.

	Ketone			Semicarbazone †		2 : 4-Dinitrophenylhydrazone †	
	Infra-red § ($cm.^{-1}$)	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$
(VII; H replaces CH_2R)	—	—	—	2650	26,500	2600	17,500
						3970	27,000
(VIII; R = H)	1705	2380	12,500	2650	26,500	2590	17,500
						3950	27,500
(VIII; R = Me)	1710	2380	12,500	2650	26,000	2605	18,500
						3980	28,500
2-*n*-Amyl-3-methyl-*cyclo*pent-2-enone ‡	—	2370	12,200	2665	20,400	—	—
	1716	Measurements in the steroid series by Jones, Williams, Whalen, and Dobriner, *J. Amer. Chem. Soc.*, 1948, **70**, 2024.					
	1675						

* Inflexion.

† Determined in chloroform solution.

‡ Gillam and West, *loc. cit.*

§ C=O frequency.

p-*Phenylazobenzoates*.

Derivative of	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$	Derivative of	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$
(V; R′ = CH_2·OH)	2300	27,000	(VI; R′ = CH_2·OH)	2320	17,000
	3245	25,000		2685	21,000
2 : 2-Dimethyl derivative of	2280	30,500		3245	23,000
(V; R′ = CH_2·OH)	3245	27,000	2 : 2-Dimethyl derivative of	2335	18,000
Ph·N_2·C_6H_4·CO_2Me-*p*	2290	11,500	(VI; R′ = CH_2·OH)	2710	21,500
	3230	23,500		3255	26,000

A few related experiments were carried out with carbinols prepared from 2 : 2-dimethyl- and 2 : 2 : 6-trimethyl-*cyclo*hexanone. Reaction between the former ketone and hex-1-ynylmagnesium bromide gave the tertiary alcohol in 75% yield. Dehydration of this compound by phosphorus oxychloride in pyridine was markedly slower than that of the unsubstituted *cyclo*hexanone analogue, but an 80% yield of hydrocarbon was obtained by using a longer reaction period. The Grignard derivative of pent-2-en-4-yne condensed with 2 : 2 : 6-trimethyl*cyclo*hexanone to furnish the alcohol in 50% yield. Very long periods of heating with phosphorus oxychloride in pyridine were necessary to dehydrate this compound, presumably owing to steric factors, but the final yield was 60%. Attempted hydration of this hydrocarbon by the boron trifluoride–methanol method gave mainly unchanged starting material, even under moderately vigorous conditions. The presence of the three ring-methyl groups clearly introduces steric factors that prevent or inhibit the approach of the hydration catalysts.

As a potential model substance for forming polyene alcohol side chains, the glycol (V; R′ = CH_2·OH) was prepared from *cyclo*hexanone and pent-2-en-4-yn-1-ol (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583). The primary hydroxyl group was protected by formation of the crystalline *p*-phenylazobenzoate; dehydration with formic acid or with phosphorus oxychloride in pyridine then gave the crystalline dehydrated ester, converted by hydrolysis into the carbinol (VI; R′ = CH_2·OH). A similar series of compounds was obtained starting from 2 : 2-dimethyl*cyclo*hexanone. No hydration was attempted with these alcohols or their derivatives.

The light-absorption properties of the compounds described in this paper are presented in the tables on p. 2655.

Experimental.

Some m. p.s [designated m. p. (K)] were taken on a Kofler block and are corrected; the remainder were taken (uncorrected) in capillary tubes. Light-absorption data were determined in ethanol solutions with a Beckman spectrophotometer unless stated otherwise.

1-*Ethynyl*cyclo*hexene* (I; R = H).—A solution of phosphorus oxychloride (55 c.c.) in dry pyridine (55 c.c.) was added slowly to a solution of 1-ethynyl*cyclo*hexanol (100 g.) in dry pyridine (150 c.c.), in a flask fitted with a stirrer and a reflux condenser, at such a rate that the mixture just boiled. After being gently heated on a steam-bath for 1 hour (internal temp., 85°), the reaction mixture was poured on ice and the product isolated with pentane. Distillation gave 1-ethynyl*cyclo*hexene (69 g., 80%) b. p. 53—56°/40 mm., n_D^{17} 1·4978. For material regenerated from the silver derivative, Milas, MacDonald, and Black (*J. Amer. Chem. Soc.*, 1948, **70**, 1829) give b. p. 52—53°/30 mm., n_D^{25} 1·4934. Material prepared by the above method did not deteriorate (in refractive index or colour) when stored over a little calcium chloride at 0° for many months.

1-1′-*Hydroxy*cyclo*hexylhex*-1-*yne* (I; R = Bu^n).—A solution of hex-1-yne (45 g.) in ether (45 c.c.) was added with stirring to an ethereal solution of ethylmagnesium bromide (from magnesium, 13·5 g.) during 30 minutes. Rapid evolution of ethane occurred after a brief induction period. Dry benzene (50 c.c.) was added to dissolve the Grignard complex, the clear solution then being stirred for 30 minutes. Purified *cyclo*hexanone (48 g.) in ether (50 c.c.) was added during 30 minutes, the flask being externally cooled with ice. After the mixture had been stirred overnight, ice and ammonium nitrate were added and the carbinol was isolated with ether. The *carbinol* (71 g., 80%) had b. p. 90—92°/1 mm., n_D^{16} 1·4836 (Found: C, 79·9; H, 11·3. $C_{12}H_{22}O$ requires C, 79·95; H, 11·2%).

Dehydration of 1-1′-*Hydroxy*cyclo*hexylhex*-1-*yne*.—(a) *With phosphorus oxychloride.* Phosphorus oxychloride (20 c.c.) in dry pyridine (50 c.c.) was added slowly with stirring to the alcohol (10 g.) in dry pyridine (20 c.c.), the mixture being kept at 20—25° by external cooling. After being kept at 25° for 30 minutes, the mixture was heated on the steam-bath for 30 minutes and then poured on excess of ice. Isolation with pentane gave 1-cyclo*hex*-1′-*enylhex*-1-*yne* (IV; R = Bu^n) (6·9 g., 80%), b. p. 68°/0·6 mm., n_D^{14} 1·5000 (Found: C, 88·7; H, 11·2. $C_{12}H_{18}$ requires C, 88·8; H, 11·2%).

(b) *With phosphorus pentachloride.* Powdered phosphorus pentachloride (14 g.) was added slowly with stirring to the alcohol (10 g.) in dry ether (70 c.c.). Stirring was continued overnight, the clear solution was then poured on ice, and the chloro-compound isolated with ether. Removal of the ether by distillation gave a residue that was heated under reflux with pyridine (50 c.c.) for 3 hours. Isolation with pentane gave the hydrocarbon (6·7 g.), b. p. 77°/0·5 mm., n_D^{17} 1·4988—1·4999.

1-n-*Hexanoyl*cyclo*hexene* (II; R = Bu^n).—(a) *By isomerisation of* (I; R = Bu^n). A mixture of the alcohol (5 g.) and formic acid (22 c.c.; *d* 1·20) was gently heated under reflux for 45 minutes. The deep green solution was poured into ice-water, and the ketone isolated with pentane. Distillation gave the nearly pure ketone (4·3 g.), b. p. 78—80°/0·5 mm., n_D^{14} 1·4843.

Treatment with semicarbazide acetate in methanol solution gave the *semicarbazone*, forming needles, m. p. (K) 173°, from aqueous methanol (Found: C, 66·1; H, 9·6. $C_{13}H_{23}ON_3$ requires C, 65·8; H, 9·8%). The 2 : 4-dinitrophenylhydrazone formed red needles (from ethanol), m. p. (K) 119° (Found: C, 60·15; H, 7·0. Calc. for $C_{18}H_{24}O_4N_4$: C, 60·0; H, 6·7%).

Hydrolysis of the semicarbazone by the method of Heilbron, Johnson, Jones, and Spinks (*J.*, 1942, 727) gave the pure ketone, b. p. 83°/0·5 mm., n_D^{16} 1·4825 (Found: C, 79·85; H, 11·2. Calc. for $C_{12}H_{20}O$:

C, 79·95; H, 11·2%). Nightingale *et al.* (*loc. cit.*) give b. p. 121—123°/18 mm., for the ketone and m. p. 118—119° for the 2 : 4-dinitrophenylhydrazone. When this isomerisation was carried out with only 10 minutes' heating the product (4·6 g.) had n_D^{17} 1·4910; treatment with semicarbazide acetate gave the foregoing semicarbazone (5·0 g.), m. p. 168° (without recrystallisation). The non-ketonic product was isolated and distilled, to yield hydrocarbon (IV; R = Bu^n) (0·5 g.), b. p. 80°/0·5 mm., n_D^{16} 1·4987.

(b) *By hydration of* 1-cyclo*hex*-1′-*enylhex*-1-*yne* (IV; R = Bu^n). (i) A solution of the hydrocarbon (5 g.) in methanol (10 c.c.) was added to a catalyst solution prepared by warming together mercuric oxide (0·3 g.), boron trifluoride–ether complex (0·1 c.c.), trichloroacetic acid (0·05 g.), and methanol (0·3 c.c.). The mixture became very warm and was then stirred for 1 hour. Isolation with ether gave the ketone (4·5 g.), n_D^{18} 1·4821. The 2 : 4-dinitrophenylhydrazone had m. p. 119°. (ii) A mixture of the hydrocarbon (2 g.), mercuric acetate (0·5 g.), ethanol (15 c.c.), water (2 c.c.), and acetic acid (2 c.c.) was heated under reflux for 3 hours. Isolation with pentane followed by distillation gave a product (0·6 g.), n_D^{17} 1·4870—1·4931, an incompletely separated mixture of starting material and the ketone. The 2 : 4-dinitrophenylhydrazone, prepared from the mixture, had m. p. 118—119°. (iii) A mixture of the hydrocarbon (1·49 g.) and formic acid (8 c.c.; *d* 1·20) was heated under reflux for 30 minutes. Isolation with pentane and distillation gave nearly pure ketone (1·41 g.), n_D^{14} 1·4848. Conversion into the 2 : 4-dinitrophenylhydrazone, purified by chromatography and crystallisation, gave the derivative (2·6 g.), m. p. 118—119°.

(c) *By condensation of* cyclo*hexene with* n-*hexanoyl chloride*. A solution of stannic chloride (62·5 g.) in redistilled carbon disulphide (150 c.c.) was cooled to −10° in a flask fitted with stirrer, thermometer, and dropping funnel. A mixture of freshly distilled *n*-hexanoyl chloride (33 g.) and *cyclo*hexene (20 g.) was added slowly with stirring, the temperature being kept below −5°. Stirring was continued at −5° for 3 hours and then at 20° for 3 hours. Ice (200 g.) was added, and the carbon disulphide removed by distillation from a steam-bath. The chloro-compound, isolated with ether, was heated under reflux with diethylaniline (38 c.c.) for 3 hours. Isolation of the product with ether, followed by two distillations, gave the ketone (18·3 g.), n_D^{17} 1·4790. The semicarbazone (m. p. 170°) and the 2 : 4-dinitrophenylhydrazone (m. p. 119°) proved to be identical with those obtained by the previous methods.

Ozonolysis of the ketone (II; R = Bu^n) by Asinger's method (*Ber.*, 1942, **75**, 656) gave a 65% yield of *n*-hexanoic acid, isolated as its *p*-phenylphenacyl ester, m. p. and mixed m. p. with an authentic sample, 67—68°.

5-1′-*Hydroxy*cyclo*hexylpent*-2-*en*-4-*yne* (V; R′ = Me).—Pent-2-en-4-yne (22 g.) in dry ether (50 c.c.) was added during 30 minutes to a solution of ethylmagnesium bromide (from magnesium, 9 g.). After a further 30 minutes' stirring, the solution was treated slowly (1 hour) with *cyclo*hexanone (33 g.) in ether (50 c.c.). Stirring was continued overnight, the solid complex then being decomposed with ice and ammonium nitrate, and the alcohol isolated with ether. Distillation gave the *alcohol* (40 g. 70%), b. p. 95—97°/1 mm., n_D^{17} 1·5173 (Found: C, 80·3; H, 9·7. $C_{11}H_{16}O$ requires C, 80·45; H, 9·8%)

5-cyclo*Hex*-1′-*enylpent*-2-*en*-4-*yne* (VI; R′ = Me).—A solution of the foregoing alcohol (17·1 g.) in pyridine (20 c.c.) was added cautiously with gentle agitation to phosphorus oxychloride (15 c.c.) in pyridine (15 c.c.) in a flask fitted with an air condenser. When the exothermic reaction had gone to completion, the mixture was allowed to cool to 20°, and the product was isolated with pentane. Distillation gave the *hydrocarbon* (13 g., 85%), b. p. 67°/1 mm., n_D^{22} 1·5468 (Found: C, 90·1; H, 9·6. $C_{11}H_{14}$ requires C, 90·35; H, 9·65%).

When a solution of the alcohol (5 g.) in formic acid (22 c.c.; *d* 1·20) was heated under reflux for 45 minutes, a mixture of the hydrocarbon and unchanged alcohol was obtained. None of the distillation fractions gave a positive ketone test with 2 : 4-dinitrophenylhydrazine.

Hydration of 5-cyclo*Hex*-1′-*enylpent*-2-*en*-4-*yne*.—(*a*) Mercuric oxide (0·6 g.) was dissolved by gentle warming in a mixture of methanol (0·6 c.c.), boron trifluoride–ether complex (0·2 c.c.), and trichloroacetic acid (0·05 g.). Methanol (5 c.c.), followed by a solution of the hydrocarbon (4·4 g.) in absolute methanol (10 c.c.), was added to the catalyst solution at 20°. The temperature of the mixture rose to *ca.* 50°, and a dark brown colour developed. After the mixture had been allowed to cool to 25°, it was filtered into sodium hydrogen carbonate solution and extracted with ether. Distillation gave a mixture (3·0 g.), b. p. 60—90°/0·4 mm., n_D^{19} 1·5361—1·5128. The total distillate was treated with semicarbazide acetate reagent, to yield a solid (1·4 g.), m. p. 170—175°, which was separated into two (still impure) components (m. p.s 163—164° and 182—183°) by recrystallisation from 80% methanol. The combined semicarbazones (1 g.) were converted directly into the mixed 2 : 4-dinitrophenylhydrazones, which were separated by chromatography on alumina. The more easily eluted 3-*ethyl*-4 : 5 : 6 : 7-*tetrahydroindan*-1-*one* (VIII; R′ = Me) 2 : 4-*dinitrophenylhydrazone* (0·96 g.) formed dark red needles (from ethanol), m. p. (K) 193° (Found: C, 59·25; H, 5·8. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·85%). Further elution gave 1-*p*,*nt*-3′-*enoyl*cyclo*hex*-1-*ene* * (VII; R′ = Me) 2 : 4-*dinitrophenylhydrazone* (0·42 g.) as vermilion plates (from ethanol), m. p. (K) 123° (Found: C, 59·2; H, 5·9. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·85%).

(*b*) The hydrocarbon (3 g.), dissolved in methanol (30 c.c.) and water (1 c.c.), was added at 20° to a catalyst solution, prepared as above from mercuric oxide (0·4 g.). The temperature slowly rose to 23°; after 5 hours at room temperature the solution was filtered into sodium hydrogen carbonate solution, and the organic products were isolated with ether. Distillation gave two major products, (i) (0·75 g.), n_D^{20} 1·5349, mainly unchanged hydrocarbon, and (ii) (1·6 g.), n_D^{20} 1·5292—1·5093, which contained ketonic material. The latter product was treated with semicarbazide acetate in methanol, to yield 3-*ethyl*-4 : 5 : 6 : 7-*tetrahydroindan*-1-*one semicarbazone*. This derivative (1·1 g.) formed needles, m. p. (K) 200—202°, from 80% methanol (Found: C, 65·15; H, 8·9. $C_{12}H_{19}ON_3$ requires

* Geneva nomenclature of the acid (CO_2H = 1).

C, 65·15; H, 8·65%). Conversion of a portion of the semicarbazone into the 2 : 4-dinitrophenylhydrazone gave a product, m. p. (K) 193°, undepressed on admixture with that obtained in the previous hydration experiment.

Hydrolysis of the semicarbazone (1 g.) gave the pure *ketone* (VIII; R′ = Me) (0·66 g.), b. p. 79—80°/0·1 mm., n_D^{18} 1·5120 (Found: C, 80·35; H, 9·75. $C_{11}H_{18}O$ requires C, 80·45; H, 9·8%).

Attempted hydration of the hydrocarbon in the presence of mercuric sulphate (cf. Nazarov and Pinkina, *loc. cit.*) or mercuric acetate led to inappreciable amounts of ketonic product, most of the starting material being recovered unchanged.

Cyclisation of the foregoing 2 : 4-dinitrophenylhydrazone (52 mg.) was effected by heating its solution in formic acid (2·5 c.c. of 90%) and phosphoric acid (0·9 g.) at 100° for 6 hours. Chromatographic purification gave one main band containing 40 mg. of material, which after recrystallisation yielded 3-ethyl-4 : 5 : 6 : 7-tetrahydroindanone 2 : 4-dinitrophenylhydrazone (32 mg.), m. p. (K) 192—193°, undepressed on admixture with an authentic specimen. Light absorption in chloroform: Maxima, 2600 and 3970 Å; ε = 18,000 and 28,000 respectively.

4-1′-*Hydroxy*cyclo*hexylbut*-1-*en*-3-*yne* (V; R′ = H).—Vinylacetylene (17·5 g.), prepared from but-3-yn-1-ol as described by Eglinton and Whiting (*loc. cit.*), was slowly distilled from a trap containing a piece of calcium chloride (for drying and to promote ebullition) into a solution of ethylmagnesium bromide (from magnesium, 7 g.) in benzene (100 c.c.). After 1 hour, *cyclo*hexanone (33 g.) in benzene (50 c.c.) was added during 30 minutes, the mixture being kept at 10°. After being stirred overnight, the resultant complex was decomposed in the usual way. Distillation gave the alcohol (30·3 g., 60%), b. p. 80—81°/2 mm., n_D^{18} 1·5170 (Nazarov *et al.* give n_D^{18} 1·5168). On cooling, the alcohol solidified; it could be recrystallised from light petroleum (b. p. 40—60°) to yield cubes, m. p. (K) 33—34°

4-cyclo*Hex*-1′-*enylbut*-1-*en*-3-*yne* (VI; R′ = H) *and its Hydration*.—This hydrocarbon was prepared as described by Nazarov and Pinkina; it had b. p. 77—79°/12 mm., n_D^{16} 1·5492 (*idem*, n_D^{18} 1·5490). Hydration by Nazarov and Pinkina's procedure gave a ketonic product, essentially (VIII; R′ = H), b. p. 83—85°/1 mm., n_D^{18} 1·5135 (*idem*, n_D^{18} 1·5155). Light absorption: Maximum, 2400 Å; ε = 11,000. The 2 : 4-*dinitrophenylhydrazone*, purified by chromatography, had m. p. (K) 246° (Found: C, 57·95; H, 5·7. $C_{14}H_{14}O_4N_4$ requires C, 58·15; H, 5·5%). Subjecting this ketone to Nazarov and Pinkina's cyclisation procedure effected little alteration in the properties of the material; it then had b. p. 84—86°/1 mm., n_D^{16} 1·5150 (*idem*, n_D^{18} 1·5146). Light absorption: see Table. The same 2 : 4-dinitrophenylhydrazone, m. p. (K) and mixed m. p. (K) 246°, was obtained. The semicarbazone crystallised from methanol as needles, m. p. (K) 210—212° (*idem*, m. p. 210°).

5-1′-*Hydroxy*cyclo*hexylpent*-2-*en*-4-*yn*-1-*ol* (V; R′ = CH_2·OH).—A solution of pent-2-en-4-yn-1-ol (10·2 g.) in benzene (100 c.c.) was added with stirring and cooling to ethylmagnesium bromide solution [from magnesium, 6·75 g., the ether being replaced by benzene (100 c.c.) after formation of the reagent]. When the exothermic reaction was complete, stirring was continued for 90 minutes, whereupon the complex had separated as a jelly. The mixture was warmed to 60° for 5 minutes with stirring, causing the complex to become a greyish-white suspension. After cooling to 20°, the stirred mixture was treated slowly with *cyclo*hexanone (12·5 g.) with external cooling. After overnight stirring, the product was isolated with ether. A viscous brown oil (18 g., 80%) was obtained: light absorption: Maximum, 2290 Å; ε = 9500. A portion was distilled at 110—130° (bath-temp., short-path still)/10^{-4} mm. giving a pale yellow liquid, n_D^{18} 1·5402.

Treatment of the glycol (0·33 g.) in pyridine (0·5 c.c.) and benzene (5 c.c.) with *p*-phenylazobenzoyl chloride (0·43 g.) gave the *mono*-p-*phenylazobenzoate*, which after recrystallisation from *iso*propanol formed orange plates (0·58 g.), m. p. 116° (Found: C, 73·95; H, 6·4. $C_{24}H_{24}O_3N_2$ requires C, 74·2; H, 6·2%).

Alkaline hydrolysis of the ester gave the pure *glycol*, b. p. 110—120° (bath-temp., short-path still)/10^{-6} mm., n_D^{17} 1·5410 (Found: C, 73·0; H, 8·8. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%).

5-cyclo*Hex*-1′-*enylpent*-2-*en*-4-*yn*-1-*ol* (VI; R′ = CH_2·OH).—A solution of the glycol mono-*p*-phenylazobenzoate (0·37 g.) in benzene (5 c.c.) and formic acid (3 c.c.; *d* 1·20) was heated under reflux for 30 minutes. After addition of water, the benzene layer was separated and chromatographed on alumina. Elution with benzene–ether (1 : 3) gave a product (0·29 g.), m. p. 97°, which when recrystallised from *iso*propanol gave 5-cyclo*hex*-1′-*enylpent*-2-*en*-4-*yn*-1-*yl* p-*phenylazobenzoate* as orange-red plates, m. p. 98—99° (Found: C, 77·55; H, 5·7. $C_{24}H_{22}O_2N_2$ requires C, 77·8; H, 6·0%). The dehydration was also readily accomplished with phosphorus oxychloride in pyridine at 70°.

Hydrolysis of this ester gave the parent *carbinol*, b. p. 60—70° (bath-temp., short-path still)/5 × 10^{-5} mm., n_D^{17} 1·5732 (Found: C, 81·15; H, 8·5. $C_{11}H_{14}O$ requires C, 81·4; H, 8·7%).

1-1′-*Hydroxy*-2′ : 2′-*dimethyl*cyclo*hexylhex*-1-*yne* (this and subsequent experiments which describe the preparation of compounds starting from 2 : 2-dimethyl*cyclo*hexanone were carried out by Mrs. A. Mende).—Hex-1-yne (9 g.) in ether–benzene (1 : 1; 20 c.c.) was added slowly at room temperature to a solution of ethylmagnesium bromide in ether (40 c.c.) (prepared from magnesium, 2·67 g.). This solution was kept for 1 hour at room temperature, whereafter 2 : 2-dimethyl*cyclo*hexanone (12·6 g.) in ether (10 c.c.) was added; a slight exothermic reaction took place and the solution became milky. After the mixture had been kept at room temperature overnight, the *alcohol* (15·5 g., 75%) was isolated in the usual way; it had b. p. 116°/2·5 mm., n_D^{16} 1·4810 (Found: C, 80·4; H, 11·4. $C_{14}H_{24}O$ requires C, 80·7; H, 11·6%).

2-*Hex*-1′-*ynyl*-3 : 3-*dimethyl*cyclo*hexene*.—1-1′-Hydroxy-2′ : 2′-dimethyl*cyclo*hexylhex-1-yne (2 g.) in dry pyridine (3 c.c.) was treated with phosphorus oxychloride (3·5 c.c.) in dry pyridine (10 c.c.), and then kept at 20° for 30 minutes. The solution was heated on the steam-bath for 3 hours and, after cooling, treated with ice, and the product isolated in pentane. Distillation gave a nearly pure product

(1·49 g., 80%), b. p. 77°/0·9 mm., n_D^{15} 1·4898. A portion of this material in pentane was chromatographed on a short column of alumina, which removed small quantities of unchanged alcohol. The pentane eluate on evaporation gave 1-6′ : 6′-*dimethyl*cyclo*hex*-1′-*enyl*hex-1-*yne*, b. p. 77°/0·9 mm., n_D^{15} 1·4912 (Found: C, 88·1; H, 11·45. $C_{14}H_{22}$ requires C, 88·35; H, 11·65%).

5-1′-*Hydroxy*-2′ : 2′-*dimethyl*cyclo*hexyl*pent-2-*en*-4-*yn*-1-*ol*.—A solution of ethylmagnesium bromide was prepared from magnesium (5·35 g.) in ether; dry benzene (80 c.c.) was then added and the ether removed by distillation. A solution of freshly distilled pent-2-en-4-yn-1-ol (8·2 g.) in benzene (40 c.c.) was added at 0° and the solution was stirred at this temperature for 2 hours. 2 : 2-Dimethyl*cyclo*hexanone (12·6 g.) in benzene (16 c.c.) was added at 0° during 30 minutes, and finally stirred at room temperature overnight (18 hours). Isolation in the usual way gave a partly crystalline product consisting of the required glycol contaminated with 2 : 2-dimethyl*cyclo*hexanone and pent-2-en-4-yn-1-ol. Most of the latter two products were removed at 80°/2 mm., and the solid residue was recrystallised from light petroleum (b. p. 60—80°) to give the glycol (4·0 g.), m. p. 87—88°. Further recrystallisation from benzene–light petroleum (b. p. 60—80°) gave the *glycol* as plates, m. p. 95° (Found: C, 75·1; H, 9·5. $C_{13}H_{20}O_2$ requires C, 74·95; H, 9·65%).

The *mono*-p-*phenylazobenzoate* of the above glycol was prepared by adding *p*-phenylazobenzoyl chloride (0·73 g.) to the glycol (0·5 g.) in benzene (10 c.c.) and pyridine (1 c.c.). After the mixture had been kept overnight at room temperature, water (3 c.c.) was added and the whole kept at 60° for 5 minutes with intermittent shaking. The solid (*p*-phenylazobenzoic anhydride) was filtered off, and the required ester isolated in the usual way. The pure *ester* (0·8 g.) crystallised from methanol as plates, m. p. 62—63° (Found: C, 75·1; H, 7·1. $C_{24}H_{32}O_3N_2$ requires C, 74·95; H, 6·75%).

Dehydration of this *p*-phenylazobenzoate (0·2 g.) was accomplished by dissolving it in pyridine (1 c.c.) and adding phosphorus oxychloride (0·4 c.c.) in pyridine (2 c.c.). The solution was heated on a steam-bath for 1½ hours, when the product was isolated with ether. Recrystallisation from methanol gave the p-*phenylazobenzoate* of 5-6′ : 6′-dimethyl*cyclo*hex-1′-enylpent-2-en-4-yn-1-ol (0·13 g.) as plates, m. p. 84—85° (Found: C, 78·55; H, 6·85. $C_{24}H_{30}O_3N_2$ requires C, 78·35; H, 6·55%).

5-1′-*Hydroxy*-2′ : 2′ : 6′-*trimethyl*cyclo*hexyl*pent-2-*en*-4-*yne*.—Pent-2-en-4-yne (11·3 g.) in dry ether (100 c.c.) was added during 30 minutes to ethylmagnesium bromide (from magnesium, 4·5 g.). The solution was then stirred at 20° for 90 minutes. 2 : 2 : 6-Trimethyl*cyclo*hexanone (23 g.) in ether (30 c.c.) was added slowly, the mixture then being stirred overnight. Isolation in the usual way gave the *alcohol* (14·8 g., 50%), b. p. 94°/0·5 mm., n_D^{17} 1·5075 (Found: C, 81·1; H, 10·55. $C_{14}H_{22}O$ requires C, 81·4; H, 10·7%).

5-2′ : 6′ : 6′-*Trimethyl*cyclo*hex*-1′-*enyl*pent-2-*en*-4-*yne*.—A mixture of the above alcohol (8·5 g.), phosphorus oxychloride (10 c.c.), and dry pyridine (15 c.c.) was heated at 70° for 24 hours. The product was isolated with pentane, the extract being passed through a column of alumina, which retained unchanged carbinol. Elution with pentane gave the *hydrocarbon* (4·4 g., 60%), b. p. 80°/0·3 mm., n_D^{18} 1·5311 (Found: C, 89·05; H, 10·5. $C_{14}H_{20}$ requires C, 89·3; H, 10·7%).

Attempted hydration of this hydrocarbon by the boron trifluoride–methanol method (50° for 2 hours) gave mainly unchanged hydrocarbon together with 20% of material, b. p. 80—83°/0·3 mm., n_D^{18} 1·5125—1·5292. Light absorption: Maximum, 2280 Å; $E_{1\,cm.}^{1\%}$ 430. No 2 : 4-dinitrophenylhydrazone could be obtained.

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590. *On Detergent–Protein Interactions.*

By E. D. GODDARD and B. A. PETHICA.

Calorimetric measurements of the heat of interaction of sodium dodecyl sulphate and bovine serum albumin have been carried out on both sides of the isoelectric point. The results have been interpreted in terms of previously reported stoicheiometric complexes. The heat data are compared with the theoretical calculations of the heats of binding.

IN many previous publications from this laboratory (Doty and Schulman; Matalon and Schulman, "Lipo-Proteins," *Discuss. Faraday Soc.*, 1949, **6**, 21, 27; Elkes, Frazer, Schulman, and Stewart, *Proc. Roy. Soc.*, 1945, *A*, **184**, 102) it has been shown that under suitable conditions soluble surface-active molecules penetrate an insoluble monolayer, causing large changes in its surface properties. In order to investigate the energetics of this type of association, it was decided to measure in bulk phase the heats of interaction between molecules similar to those studied by the penetration technique. The results obtained will be published later in full, but

one of interest will be quoted here: on the acid side of the isoelectric point, serum albumin very readily penetrates the negatively charged monolayer, sodium behenyl sulphate, but on the alkaline side only very slightly. This was to be expected on the basis of inter-ionic forces of attraction and repulsion. However, it is known that serum albumin and sodium dodecyl sulphate interact in solution on the alkaline side of the isoelectric point, giving soluble complexes. Therefore attention was turned to a calorimetric investigation of this association, as well as of the precipitation on the acid side.

In recent years, a large number of investigations on the interactions of proteins and anions have been published (Murray Luck, *Discuss. Faraday Soc.*, 1949, **6**, 44). The interactions have been studied by ultra-filtration, dialysis equilibrium, electrophoresis, and absorption-spectrum techniques. An approach to the evaluation of the energetics of these interactions was first made by Klotz (*Arch. Biochem.*, 1946, **9**, 109) on the basis of the law of mass action, and modified so as to allow for the electrostatic contribution to the free energy of binding of successive anions to the protein (Scatchard, Scheinberg, and Armstrong, *J. Amer. Chem. Soc.*, 1950, **72**, 535, 540; Klotz, Walker, and Pivan, *ibid.*, 1946, **68**, 1486). A further modification to the simple theory was put forward to allow for the heterogeneity of reaction sites on the protein, a Gaussian distribution of the intrinsic binding constants being proposed for the combination of serum albumin and alkyl sulphates (Karush and Sonenberg, *ibid.*, 1949, **71**, 1369). Karush (*ibid.*, 1950, **72**, 2705), however, showed that two simple types of adsorption site could account for the interaction of an azo-dye with albumin. On the basis of these various interpretations of the protein–anion equilibrium, a number of values of the heats, free energies, and entropies of the binding processes have been given. No direct measurements of the heats of these interactions have been made. It is the purpose of this communication to provide data on one such interaction, *viz.*, that between bovine serum albumin and sodium dodecyl sulphate, which has been extensively studied by other methods (Putnam, *Adv. Protein Chem.*, 1948, **4**, 79).

Experimental.

The calorimeter (Fig. 1) consists of a silvered Dewar vessel provided with an observation window, and closed by a well-fitting thick cork. The cork carries a glass stirrer (*A*) driven by a governor-controlled induction motor at 60 r.p.m. The protein solutions were placed in the vessel, and the detergent solutions in a partly immersed bulb (*B*) firmly held in position by a collar (*C*). *D* and *E* represent thermistors and heater respectively; *F* is the breaker support (B.14 joints). The vessel was placed in a water thermostat at 25°. Mixing was effected by breaking the bulb (*B*). Several breaking techniques were tested, and the following practical points emerged: (i) no alteration in liquid levels must occur, and the meniscus inside and outside the bulb should coincide, and be at the wide part of the bulb; (ii) the top of the bulb should be thick, in order to prevent cracking of the glass above the liquid; (iii) the breaker is best operated from within the bulb (*B*), and its level should remain constant; (iv) the re-entrant gossamer area of the bulb is best set opposite the stirrer for rapid mixing on breaking; (v) the thermistors should be set as far as possible from the stirrer and bulb in order to avoid variable eddy currents.

Two glass-protected thermistors (type F, Standard Telephones and Cables Ltd.; Sillars, *J. Sci. Instr.*, 1942, **19**, 81) were used, of total resistance 3700 Ω at 24°. The thermistors were one arm of a Wheatstone bridge, which had arms in the ratio 10 : 4. With this ratio, the variation of resistance of the thermistors was read on the balance arm as 370 Ω/°c. at 24°. This could be read to 0·1 Ω, giving a sensitivity of the instrument of $2{\cdot}7 \times 10^{-4}$°.

The materials used were crystallised bovine serum albumin (Armour), and pure sodium dodecyl sulphate (Verley). The high purity of the sulphate was confirmed by observing that the surface tension–concentration curve showed no minimum. The buffers used were: (*a*) pH 6·8: 0·025M-Na_2HPO_4, 0·025M-NaH_2PO_4, 0·1M-NaCl; and (*b*) pH 4·3: 0·1M-$CH_3{\cdot}CO_2Na$, 0·2M-$CH_3{\cdot}CO_2H$. 110 Ml. of protein solution and 20 ml. of detergent solution were used in each experiment. At pH 6·8, 1·0 g. of the protein was used, and at pH 4·3, 0·5 g. After assembly, the system was left for 3—4 hours at 23·5°, to reach thermal equilibrium. Resistance readings were then taken until a steady drift with time was observed for 15—30 minutes, then the reagents were mixed. The new drift was measured until steady, whereupon the calibrating current was passed. The energy generated by the heating coil was measured by means of a standard ammeter and voltmeter. A typical run is represented in Fig. 2.

Results and discussion.

The results of the heat determinations are shown in Fig. 3 for pH 4·3 and 6·8. The heats of reaction are small, and the temperature measurements are subject to considerable error at the lower end of the scale. The results are all subject to a possible error of $\pm 0{\cdot}05$ cal. per g. of protein, which represents the sensitivity of the instrument. The reliability of the bulb-breaking technique was tested in a series of eight blank runs. Six showed no temperature change on breaking and two a temperature change corresponding to a negative heat (expressed as cals./g. of protein) of 0·18 and 0·20 cal. It appears then, that there is an occasional systematic error

in one direction, and it is therefore possible that individual determinations are low by approximately 0·20 cal. This is of importance mainly at the lower detergent : protein ratios. In view of the very small temperature changes involved, we feel that these results are worthy of record, and would be difficult to improve.

Examination of the results at pH 6·8 shows a double inflection at detergent : protein ratios of 0·23 and 0·45. These inflections correspond to the electrophoretically homogeneous complexes between sodium dodecyl sulphate and serum albumin reported by Putnam and Neurath (*J. Biol. Chem.*, **1945**, **159**, 195) and denoted as AD_n and AD_{2n}, n being approximately 55 in terms of molecules of sodium dodecyl sulphate per albumin molecule (a molecular weight of 70,000 being assumed for albumin). Diffusion experiments on these two complexes gave values of molecular weights which approximated to those expected on the assumption that all the detergent was bound to the protein (*idem*, *ibid.*, **1945**, **160**, 397). These workers found that sodium dodecyl sulphate in excess of the AD_{2n} was bound, but that these higher complexes dissociated during electrophoresis. It is generally assumed that the detergent is bound to the

FIG. 1.

The calorimeter.

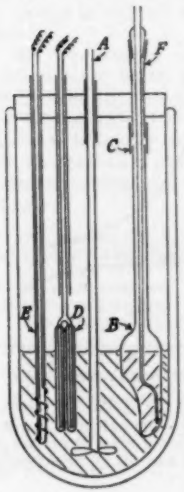
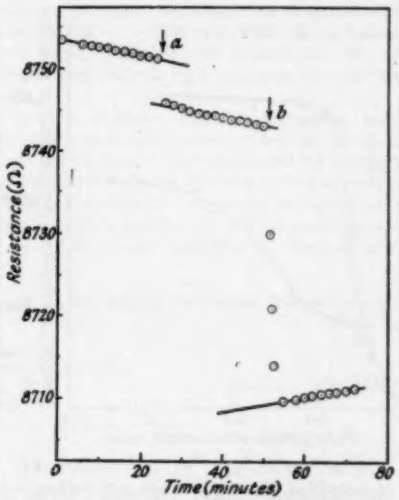


FIG. 2.



Resistance–time readings of a typical run. Reagents mixed at (a), *and heater switched on for* 2 *minutes at* (b). *Reaction of* 1·00 *g. of serum albumin and* 1·00 *g. of sodium dodecyl sulphate at* pH 6·8.

cationic groups of the protein. Several analyses have given the number of these cationic groups as 100—110 per serum albumin molecule (Tanford, *J. Amer. Chem. Soc.*, 1950, **72**, 441; Stein and Moore; *J. Biol. Chem.*, **1949**, **178**, 79; Brand, *Ann. N.Y. Acad. Sci.*, 1946, **47**, 187). Lundgren (*Adv. Protein Chem.*, **1949**, **5**, 305) found that extraction of egg albumin–dodecyl benzenesulphonate mixtures with 60% acetone removed detergent in excess of that bound to the cationic groups of the protein. The remainder could only be removed by addition of inorganic salt to the mixture. The experiments reported here at pH 6·8 support these explanations of the albumin–sodium dodecyl sulphate reaction, the heats of reaction falling into three groups: (*a*) a linear portion up to the complete formation of AD_n, with an enthalpy change on formation of AD_n from protein and detergent under these conditions of −1250 cals./mole of sodium dodecyl sulphate; (*b*) a " plateau " corresponding to the reaction $AD_n + nD = AD_{2n}$, $-\Delta H = 230$ cals./mole of sodium dodecyl sulphate; (*c*) a further rise, corresponding to the further binding of detergent, probably reaching a maximum around 1·5 g. of detergent per g. of protein. The initial part of the third stage gives a heat of binding ($-\Delta H$) of 960 cals./mole of sodium dodecyl sulphate. From viscosity data (Neurath and

Putnam, *J. Biol. Chem.*, 1945, **160**, 397; Putnam and Neurath, *J. Amer. Chem. Soc.*, 1944, **66**, 1992), it is concluded that irreversible denaturation occurs on binding of the sodium dodecyl sulphate beyond the AD_n stage (see also Lundgren and O'Connell, *Ind. Eng. Chem.*, 1944, **36**, 370).

The results of the investigation of the range of precipitation of serum albumin with sodium dodecyl sulphate (Putnam and Neurath, *J. Amer. Chem. Soc.*, 1944, **66**, 692) show that maximum precipitation occurs in the range from AD_n to AD_{2n} at acid pH. The re-dissolution of the initially formed precipitate in the region of detergent excess can be explained in terms of the building up of a second detergent layer on the protein, with the polar groups directed outwards (Pankhurst, " Surface Chemistry," Butterworth, London, 1949, p. 109).

The interpretation of the heat data at pH 4·3 is difficult, since heats of precipitation are involved over the range of detergent : protein ratios from 0·1 to 0·5, and the heats of solution of the complexes AD_n and AD_{2n} are unknown. Several important results emerge. First, that

FIG. 3.

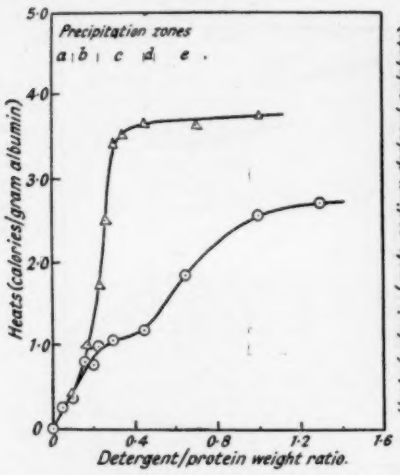


FIG. 4.

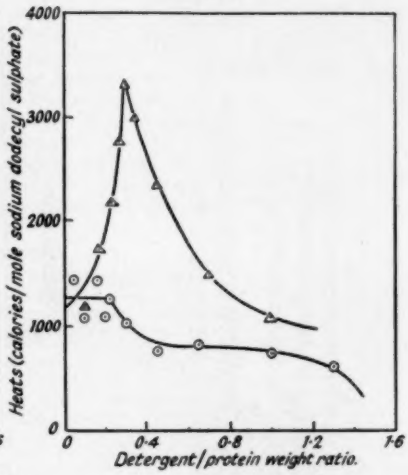


FIG. 3.

The heats of interaction of serum albumin and sodium dodecyl sulphate. ⊙ *At* pH 6·8; △ *at* pH 4·3. *The heats are given as* $-\Delta H$, *in cals. per g. of albumin. The precipitation zones at* pH 4·3 *are taken from Putnam and Neurath's data.* (a) *and* (e), *no precipitation*; (b) *and* (d), *partial precipitation*; (c), *complete precipitation.*

FIG. 4.

The heats of interaction of serum albumin and sodium dodecyl sulphate. △ *At* pH 6·8. ▲ *At* pH 4·3. *The heats are given as* $-\Delta H$ *in cals. per mole, of sodium dodecyl sulphate.*

where precipitation is small (up to a ratio of 0·1), the heat of reaction is independent of pH from pH 4·3 to pH 6·8. It would appear from Fig. 3 that the heat of interaction at pH 4·3 in region (*e*) is compensated by the approximately equal heat of solution of the precipitate, and the overall heat measured in this range remains constant. In Fig. 4 the results are plotted as overall heats of reaction per mole of sodium dodecyl sulphate versus the detergent : albumin weight ratio. At pH 6·8, this method of plotting confirms the three stages of the interaction. At pH 4·3 a sharp maximum occurs at a ratio of 0·3 in the range of maximum precipitation of the protein, in which denaturation occurs.

Estimations of the heat of binding to serum albumin have been made for a number of anions on the alkaline side of the isolectric point. Klotz and Urquhart (*J. Amer. Chem. Soc.*, 1949, **71**, 847) give ΔH −2100 cals./mole for methyl-orange, and −2000 for azosulphathiazole. Scatchard, Scheinberg, and Armstrong give a positive ΔH of 430 ± 540 cals./mole for the chloride ion (*ibid.*, 1950, **72**, 535), and a zero heat for the thiocyanate ion (*ibid.*, p. 540). Karush and Sonenberg (*ibid.*, 1949, **71**, 1369) found for sodium decyl sulphate that the heat of binding

($-\Delta H$) is 2000 cals./mole. They report the surprising result that the heats of binding of sodium octyl and dodecyl sulphates are zero. Our direct measurements give $-\Delta H$ 1250 cals./mole for dodecyl sulphate over the range studied by Karush and Sonenberg. A possible source of the discrepancy is that in Karush and Sonenberg's work the long-chain sulphates were always below the micelle points. In ours the detergent was always above the micelle point before the reaction in the AD_n range and below it after the mixing. A correction should therefore be made for the heat of formation of the sulphate micelles. A number of tests were made to measure the heat of formation of sodium dodecyl sulphate micelles, by dilution of a micellar solution of the salt in the calorimeter. The number of micelles destroyed in the dilution process could be calculated from a knowledge of the critical micelle point (Corrin and Harkins, *ibid.*, 1947, **69**, 687). A mean result of our experiments gave a heat of formation of the micelles from free molecules ($-\Delta H$) as 250 cals./mole of sodium dodecyl sulphate, but this could not be statistically distinguished from zero. Data were collected by Stainsby and Alexander (*Trans. Faraday Soc.*, 1950, **46**, 587) on the temperature dependence of critical micelle points of a number of soaps. From these a value of $\Delta H = -250$ cals./mole of sodium dodecyl sulphate was calculated for the formation of micelles at 24°. Correction of the heat of formation of AD_n for the destruction of detergent micelles in our experiments would, in any case, change the value previously quoted to $\Delta H = -1500$ cals./mole of sulphate, thereby increasing the divergence of these results from those of Karush and Sonenberg. We conclude, therefore, that it is difficult to reconcile Karush and Sonenberg's calculations with our direct measurements.

Since the free energy of binding of sodium dodecyl sulphate to serum albumin is large ($-\Delta G = 7$—10 kcals. for the first detergent molecule bound; Murray Luck, *loc. cit.*; Karush and Sonenberg, *loc. cit.*), the binding of the detergent is accompanied by a large increase in entropy, *viz.*, *ca.* 18—28 e.u. per mole of dodecyl sulphate for the first molecule bound. This entropy increase is usually ascribed either to disorientation in the protein or to loss of water of solution on the formation of the ionic detergent–protein bonds. A critical re-evaluation of the thermodynamic treatment of protein–ion equilibria seems desirable in view of the results presented here.

We are indebted to Dr. J. H. Schulman, O.B.E., for helpful discussions and advice, and to the Elsie Ballot Trust for a scholarship to one of us (E. D. G.).

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591. *An X-Ray and Thermal Examination of the Glycerides. Part XI.* The 1 : 2-Diglycerides, and Further Observations on 1 : 3-Diglycerides.*

By R. J. Howe and T. Malkin.

1 : 2-Diglycerides of lauric, myristic, palmitic, and stearic acids are shown to exist in two solid modifications, α and β, for which *X*-ray and m. p. data are reported. The transition $\alpha \rightarrow \beta$ is much slower than was found for the more symmetrical 1 : 3-isomers (Part III, *J.*, 1937, 1409). Earlier data for 1 : 3-diglycerides have been extended and reviewed in the light of recent work by Baur, Jackson, Kolp, and Lutton (*J. Amer. Chem. Soc.*, 1949, **71**, 3363).

Our synthetic work on phospholipids (following paper) necessitated the preparation of a series of 1 : 2-diglycerides, and since there does not appear to be any information concerning their polymorphism, we have examined them by means of *X*-rays and cooling and heating curves, in the manner described in Parts I and II (*J.*, 1934, 666; 1936, 1628).

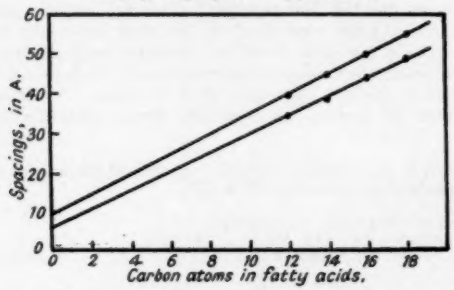
The preparation of these compounds in good yield is a matter of some difficulty, owing to the facile migration of the 2-ester group to the 1(3)-position, particularly in the presence of traces of acids, first shown by Fischer (*Ber.*, 1920, **53**, 1621) who, indeed, took advantage of this migration in his preparation of 1 : 3-diglycerides *via* the intermediate 1 : 2-isomer. This should, therefore,

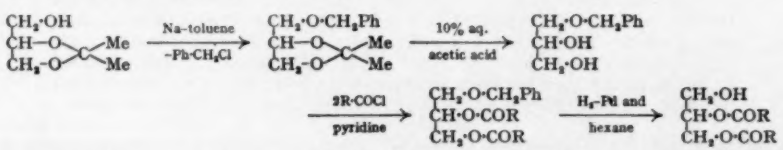
* Part X, *J.*, 1949, 369.

be borne in mind when considering any preparation and description earlier than Fischer's paper (cf. Fairbourne, *J.*, 1930, 368, who reviewed earlier work). The only satisfactory methods of preparation involve (1) protection of one primary hydroxyl of glycerol, (2) complete acylation, (3) removal of the protecting group by catalytic hydrogenolysis. Verkade *et al.* (*Proc. Akad. Wetensch., Amsterdam*, 1937, **40**, 580; *Rec. Trav. chim.*, 1940, **59**, 1123) effected protection with the trityl group, which was removed with a specially activated palladium-black. We find this hydrogenolysis capricious, as did Daubert and King (*J. Amer. Chem. Soc.*, 1939, **61**, 3328). Moreover, removal of the solid by-product, triphenylmethane, by crystallisation reduces the yield, particularly with lower members of the series (C_{14} and C_{12} acids). Daubert and King avoided this by protection with the carbobenzyloxy-group, which, on hydrogenolysis, is converted into toluene, but unfortunately the intermediate carbobenzyloxyglycerol decomposes on distillation, and is therefore difficult to obtain pure. More recently, Sowden and Fischer (*ibid.*, 1941, **63**, 3244) used the 1-benzyl ether of glycerol in the preparation of optically active 1 : 2-diglycerides, and with certain modifications this method gives excellent results. Sowden and Fischer refluxed *iso*propylidene glycerol with powdered sodium over ether for 20 hours, and converted the resulting sodium derivative into the benzyl ether in a yield of 66% by a further 70 hours' refluxing with three molecular proportions of benzyl chloride. The time was shortened and the yield increased to 70% and later to 78% by Baer and Kates (*ibid.*, 1950, **72**, 942) by the use of a sodium–naphthalene reagent (cf. Scott, Walker, and Hansley, *ibid.*, 1936, **58**, 2442; 1938, **60**, 951). We now find that by using for the preparation of benzyl ethers the general method of Van Duzee and Adkins (*ibid.*, 1935, **57**, 147), which involves the use of powdered sodium under toluene, yields of 80—85% of the benzyl ether can be obtained in a few hours, only one molecular proportion of benzyl chloride being used. The yield in the next stage is also improved by using 10% aqueous acetic acid to remove the *iso*propylidene group, a method used by Baer and Fischer (*ibid.*, 1945, **67**, 2031) in their preparation of monoglycerides. Our method of preparation is outlined below :

FIG. 1.

Long spacings of 1 : 2-*diglycerides.*



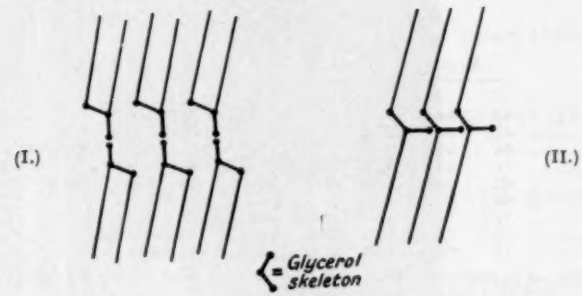


Thermal Examination.—Capillary m. p.s, and cooling and heating curves, show the existence of two solid modifications, a lower-melting α-form and the stable β-form. Solvent-crystallised material melts at the β m. p., and resolidifies at the α m. p., remelting again at the α m. p. The change α → β is very slow, but keeping of α-forms just below their m. p.s overnight brings about the change. Cooling and heating curves normally show only the α m. p. arrests. This behaviour is in sharp contrast to that of the symmetrical 1 : 3-diglycerides, the α-forms of which change so rapidly into β′-forms that their existence can only be indirectly inferred (Part III, *J.*, 1937, 1412). 1 : 2-Diglycerides show spherulite formation when solidified under a cover slip

and viewed between crossed Nicols, but the rippled appearance characteristic of 1 : 3-diglycerides is absent (cf. Part III).

X-*Ray Examination.*—This offered no special difficulty, owing to the relative stability of the α-forms. Long spacings of α- and β-forms were obtained from melted and pressed layers, respectively, and side spacings from thin rods. The long spacings, when plotted against the carbon content of the fatty acid component, fall on two straight lines which cut the axis, C = 0, at ≏ 6·5 and 9·5 A. (Fig. 1). These results best agree with an arrangement of double molecules Fig. 2 (I) lying vertically across (α-form) or inclined at an angle of ≏ 64° (β-form) to the reflecting planes, on the assumption of an angle of 116° between the carbon atoms of the chain. The magnitude of both the α-spacing and the intercepts at C = 0 would appear to rule out an arrangement of single molecules Fig. 2 (II). The side spacings of the α-forms are, within experimental error, identical for the series, and those of the β-forms, although differing slightly

FIG. 2.



Diagrammatic.

amongst themselves, are all of the same type, and quite distinct from those of the 1 : 3-isomers (see Plate, facing p. 2666, and Table I).

1 : 3-*Diglycerides.*—In Part III (*J.*, 1937, 1412), it was shown that the majority of a series of 1 : 3-diglycerides, from didecoin to distearin, existed in both β- and β′-modifications, but that there appeared to be a discontinuity at dipentadecoin, since only one β-form was observed for the higher members. Certain anomalies were also noted regarding the type of side spacings associated with each form, for which no satisfactory explanation could be offered at the time. Considerable light has been thrown on this problem by the recent results of Baur, Jackson, Kolp,

TABLE I.

M. p. and X-*ray data for* DL-1 : 2-*diglycerides.*

	α-Form.			β-Form.				
	M. p.	Long spacing, A.	Side spacing, A.	M. p.	Long spacing, A.	Side spacing, A.* m.	vs.	s.
Dilaurin	20·0°	39·2	4·13	39°	34·1	4·31	4·01	3·79
Dimyristin	37·5	44·4	4·12	54, 59 [2]	38·8	4·31	4·06	3·82
Dipalmitin	50·0	49·3	5·10	63·5, 65—66,[2] 64 [3]	43·5	4·27	4·03	3·76
Distearin	59·5	54·5	4·12	71, 68·5—69 [1] 71·5—72·5 [2]	48·3	4·27	4·05	3·81

[1] Verkade *et al.*, *loc. cit.* [2] Baer and Kates, *loc. cit.* [3] Daubert and King, *loc. cit.*
* m = moderate; vs = very strong; s = strong.

and Lutton (*J. Amer. Chem. Soc.*, 1949, **71**, 3363), who have now observed the missing β-forms for dipalmitin and distearin, and have shown that these compounds frequently crystallise from solvents in the β′-forms, which change into the stable β-forms only when held near the β′ m. p. These results made it clear that there are β′- and β-forms for the whole series; but there still remained some confusion regarding the side spacings. Thus, Baur *et al.* observed two distinct types of side spacings : *a*-type (4·6, v. strong; 3·9, mod.; 3·7, strong) and *b*-type (4·6, v. strong; 3·75, strong), neither of which quite agrees with those described by Malkin and Shurbagy

(Part III, *loc. cit.*), *viz.*, *a*-type (4·6, strong; 3·9, strong; 3·73, strong) and *b*-type (4·6, strong; 3·9, weak; 3·73, strong; 3·6, weak), although there are many points of similarity. Because of these differences, we have re-examined the whole problem, and it appears that there are, in fact, three distinct types of side spacings, *viz.*, the *a*- and *b*-types described in Part III, and the new type observed by Baur *et al.*, which we term *c*-type (Plate, Figs. 6, 7, 8). These occur as follows :

a-Type : β-forms of all odd-acid diglycerides, β′-forms of dipalmitin and distearin.

b-Type : β′-forms of all diglycerides except dipalmitin and distearin.

c-Type : β-forms of all even-acid diglycerides.

b-Type spacings are sometimes very similar to *a*-type, but the latter are distinguished by the equal intensity of the three main lines (see Plate, Fig. 6, *a*-type, and Figs. 9, 10, 11, *b*-type).

M. p. and *X*-ray data for the whole series are given in Table II.

TABLE II.

M. p. and X*-ray data for* 1 : 3*-diglycerides.*

	M. p.		Long spacings, A.		Side spacings, A.*				
	β′.	β.	β′.	β.	β′.			β.	
Didecoin	42°	44·5°	30·5	32·5	*b* 4·65s, 3·93m, 3·7s, 3·46w	*c* 4·55			3·75
Diundecoin	47	49	33·2	35·2	*b* 4·63s, 3·88w, 3·72s, 3·58w	*a* 4·53	3·81		3·66
Dilaurin	54	56·5	35·7	37·4	*b* 4·66s, 3·94m, 3·73s, 3·61vw	*c* 4·6			3·75
Ditridecoin	57	59·5	38·1	40·4	*b* 4·58*s*. 3·9w, 3·71s, 3·53w	*a* 4·55	3·83		3·68
Dimyristin	63	65·5	40·5	42·6	*b* 4·64s, 3·88m, 3·68s, 3·53vw	*c* 4·57			3·73
Dipentadecoin	66·5	68·5	42·5	45·0	*b* 4·58s, 3·86w, 3·70s, 3·52w	*a* 4·58	3·84		3·68
Dipalmitin	71·5	72·5	44·7	47·5 †	*a* 4·6s, 3·87s, 3·65s	*c* 4·6			3·75
Diheptadecoin	72·5	74·5	47·7	50·3	*b* 4·6s, 3·85m, 3·7s, 3·54w	*a* 4·57	3·82		3·66
Distearin	77	78	49·5	52·8 †	*a* 4·6s, 3·88s, 3·68s	*c* 4·6			3·73

* s = strong; *m* = moderate; w = weak; vw = very weak. All β-side spacings are strong.
† Baur *et al.* find 47·4 and 52·8, respectively.

EXPERIMENTAL.

iso*Propylidene Glycerol* 1-*Benzyl Ether*.—Sodium (11·5 g., 0·5 g.-atom) was granulated under boiling toluene by vigorous stirring, and then cooled, and *iso*propylidene glycerol (Part III, p. 1634) (76 g., 0·58 g.-mol.) was added, in portions, with stirring. The reaction, which was at first vigorous, subsided after a time, and was completed by boiling the toluene to break up unattacked sodium. All the latter had reacted in about an hour. Benzyl chloride (63·25 g., 0·5 g.-mol.) was then added to the gently refluxing, stirred solution during ½ hour, and the heating continued for a further hour. After cooling, precipitated sodium chloride was filtered off and washed with toluene, and after removal of toluene under reduced pressure, the residue was distilled *in vacuo*, yielding a few grams of unchanged benzyl chloride and *iso*propylidene glycerol, boiling up to 110°, and 86·5 g. (78%) of the benzyl ether, b. p. 117—121°/3 mm. Sowden and Fischer (*loc. cit.*) give b. p. 93—96°/0·1 mm.

Glycerol 1-*Benzyl Ether*.—The above *iso*propylidene glycerol ether (17·65 g.) was heated on a boiling-water bath with 10% acetic acid (45 c.c.) with frequent shaking, until the original emulsion had disappeared (2 hours). Acetic acid, water, and acetone were then removed under reduced pressure, and the residue distilled *in vacuo* to yield the glycerol 1-benzyl ether (13 g., 87%), b. p. 140—145°/1 mm.

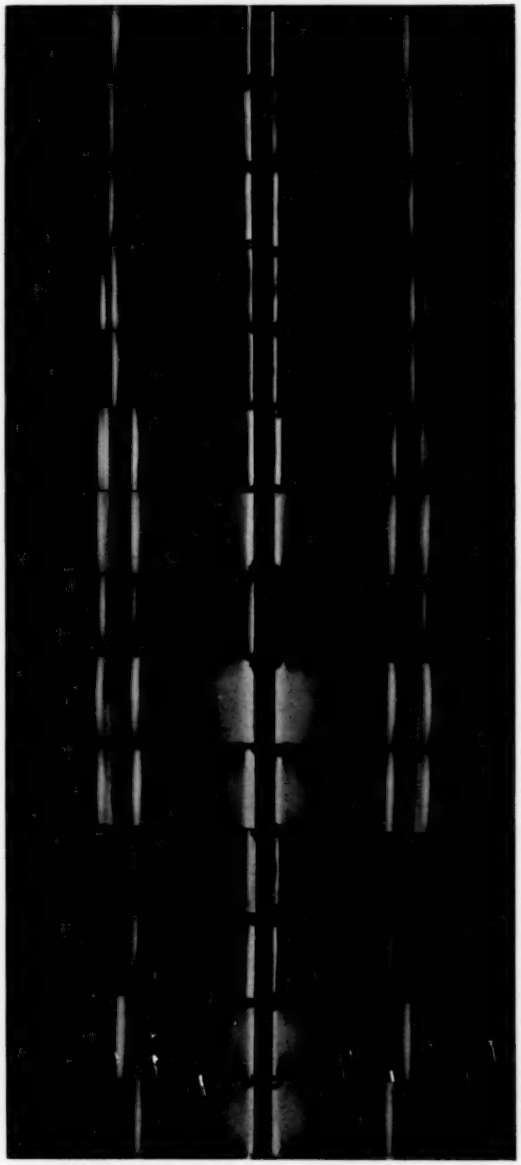
3-Benzyl 1 : 2-*Dipalmitoyl Glycerol*.—The acylation of glycerol 1-benzyl ether followed standard practice and will be described in detail for the dipalmitoyl derivative only. Acid chlorides were prepared by Bauer's method (*Oil and Soap*, 1946, **23**, 1), thionyl chloride being used except for stearic acid, where it is preferable to use oxalyl chloride.

A solution of palmitoyl chloride (16·6 g., 0·03 g.-mol.) in dry carbon tetrachloride (20 c.c.) was added to a mixture of glycerol 1-benzyl ether (5·45 g., 0·03 g.-mol.) and pyridine (4·8 g., 0·03 g.-mol.), dissolved in the same solvent (40 c.c.). The solution became warm, and pyridine hydrochloride separated. After this had been kept overnight at 40°, ether was added, and the ethereal solution was washed successively with 1% aqueous hydrochloric acid, saturated sodium hydrogen carbonate, and water. After drying (Na_2SO_4) and removal of solvent, the solid residue was crystallised twice from ethanol, to yield colourless needle-like crystals (17·5 g., 88%), m. p. 44—45·5°. Baer and Kates (*loc. cit.*) give 48% yield, m. p. 45—46°.

The following 3-benzyl glycerols were prepared in a similar manner : 1 : 2-*Dilauroyl* (78% yield), m. p. 20—21° (Found : C, 74·8; H, 10·9. $C_{34}H_{58}O_5$ requires C, 74·7; H, 10·7%); 1 : 2-*dimyristoyl* (80% yield), m. p. 35—36·5° (Found : C, 75·6; H, 10·9. $C_{38}H_{66}O_5$ requires C, 75·7; H, 11·0%); 1 : 2-distearoyl (83% yield), m. p. 53—55°. These acylations could also be carried out in benzene.

1 : 2-*Dipalmitin*.—The dipalmitoyl intermediate (5 g.), dissolved with gentle warming in *n*-hexane (40 c.c.), and palladium-black (1 g.) (Johnson, Matthey and Co.) were shaken in an atmosphere of hydrogen, until hydrogen uptake, which was at first rapid, had ceased (2 hours) (Found : uptake, 350 c.c. Calc. : 172 c.c.). The dipalmitin was precipitated during hydrogenation in shiny

FIG



1. α-*Form*, 1 : 2-*dipalmitin*.
2. β-*Form*, 1 : 2-*dilaurin*.
3. β-*Form*, 1 : 2-*dimyristin*.
4. β-*Form*, 1 : 2-*dipalmitin*.
5. β-*Form*, 1 : 2-*distearin*.
6. a-*Type* (β-*form of* 1 : 3-*ditridecoin*).
7. b-*Type* (β′-*form of* 1 : 3-*ditridecoin*).
8. c-*Type* (β-*form of* 1 : 3-*dimyristin*).
9. β′-*Form of* 1 : 3-*didecoin*.
10. β′-*Form of* 1 : 3-*dilaurin*.
11. β′-*Form of* 1 : 3-*dimyristin*.
12. β′-*Form of* 1 : 3-*dipalmitin*.
13. α-*Kephalin* (*dipalmitoyl*).
14. β-*Kephalin* (*dipalmitoyl*).

To face p. 2666.

crystals, easily distinguishable from the less crystalline intermediate. After the hydrogen in the apparatus had been displaced by air, the diglyceride was dissolved by warming the solution, and the catalyst was filtered off and washed with hot hexane. On cooling, the solution deposited dipalmitin (4 g., 93%), m. p. 63—64° not improved by further crystallisation. Yields for other members were: *dilaurin* (Found: C, 71·2; H, 11·3. $C_{27}H_{52}O_5$ requires C, 71·0; H, 11·5%), 80%; dimyristin (Found: C, 72·6; H, 11·8. Calc. for $C_{31}H_{60}O_5$: C, 72·7; H, 11·8%), 83%; distearin, 85%. Compared with other members, the m. p. of dimyristin given by Daubert and King (*loc. cit.*) is unusually high. The same catalyst could be used repeatedly if well washed with hexane, an advantage in view of the large amount required.

We thank the Royal Society and the Colston Society for grants, and gratefully acknowledge generous gifts of highly purified fatty acids from the Research Department of Lever Bros. and Unilever Ltd., and from Messrs. Price's (Bromborough) Ltd.

THE UNIVERSITY, BRISTOL, 8. [*Received, April 30th*, 1951.]

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592. *An X-Ray Examination of Synthetic (±)-α- and β-Kephalins.*

By T. H. BEVAN and T. MALKIN.

Long and side spacings are given for synthetic dilauroyl, dimyristoyl, dipalmitoyl, and distearoyl (±)-α- and β-kephalins (phosphatidylethanolamines). The data agree with an arrangement of double molecules lying across the reflecting planes at angles of ≏73° 20′ (α-compounds) and 55° 5′ (β-compounds). The side spacings readily distinguish between the (±)-α- and the β-isomer.

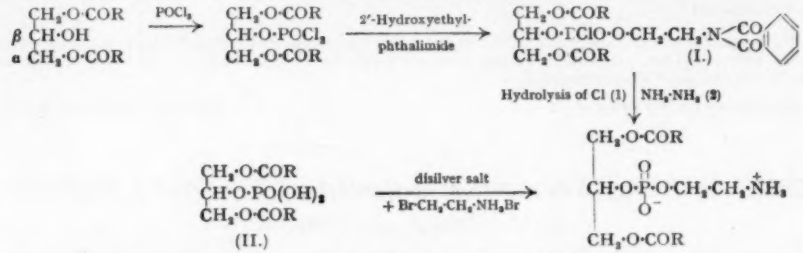
THE present investigation was undertaken in order to obtained data to identify the natural kephalins, and also to establish the position of the phosphate group. Chromatographic work is in hand (cf. *J.*, 1951, 841) which we hope will shortly yield suitable natural specimens for comparison.

For the more fully investigated lecithin, it would now appear that the phosphate group is exclusively in the α-position of the glycerol molecule. α-Lecithin has long been known to exist, because of the isolation, from its products of hydrolysis, of optically active glycerophosphoric acid, which must, of course, be the α-acid. Similarly, the isolation of β-glycerophosphoric acid (Karrer and Salomon, *Helv. Chim. Acta*, 1926, **9**, 3) has been considered as proof of the existence of β-lecithin. Baer and Kates (*J. Biol. Chem.*, 1948, **175**, 79; 1950, **185**, 615) have, however, shown that acid and alkaline hydrolysis of α-lecithin give rise to both α- and β-glycerophosphoric acid, owing to the migration of the phosphate group. Consequently, the isolation of β-glycerophosphoric acid cannot be regarded as proof of the existence of β-lecithin. Further, they have shown (*J. Amer. Chem. Soc.*, 1948, **70**, 1394) that the *X*-ray diffraction patterns of synthetic (−)-α-dipalmitoyl-lecithin and natural dipalmitoyl-lecithin are identical.

The position with regard to kephalin is much less definite; from its close biological and chemical relationship to lecithin, it might also be expected to have the α-structure, a view which is supported by its reported optical activity (Levene and Rolf, *J. Biol. Chem.*, 1919, **40**, 1). This, however, could well be due to admixture with lecithin, with which it is invariably associated, or with sugars (Hutt *et al.*, *Nature*, 1950, **165**, 314). Folch (*J. Biol. Chem.*, 1942, **146**, 35), who claims to have prepared kephalin "in a relative state of purity for the first time," makes no reference to its optical activity and, unfortunately, also omits to indicate which glycerophosphoric acid it affords on hydrolysis. The recent statement by Rose (*J. Amer. Chem. Soc.*, 1947, **69**, 1384), that the long spacings of synthetic β-kephalin and natural kephalin are similar, would appear to be in favour of the β-structure but, as no details are given, it can be accepted only with reserve. With an *X*-ray comparison, one would expect either identity or non-identity, rather than the somewhat indefinite "similarity." It is surprising, too, that no mention is made of the side spacings, which are usually a prominent feature of the *X*-ray photographs.

Our kephalins were prepared by Rose's method (*loc. cit.*), outlined below. We adopted Hunter, Roberts, and Kester's modification (*J. Amer. Chem. Soc.*, 1948, **70**, 3244), which consists in carrying through the synthesis to the end, without isolation of the intermediate phthalimide derivative (I), and which, by avoiding emulsion and crystallisation losses, results in a considerably increased yield. We found an equal improvement in yield when Rose's alternative method (using carbobenzyloxyethanolamine) was similarly carried through to the

end, but we preferred the phthalimide method because of the higher yield, and also because of the unavailability of phosphonium iodide, which Rose used for removing the carbobenzyloxy-group. It is noteworthy that, although Rose was unable to remove the latter group by catalytic hydrogenolysis, Baer, Marukas, and Russell (*Science*, 1951, **113**, 12) have now succeeded in doing so, from a series of diacyl α-glycerylphenylphosphorylcarbobenzyloxyethanolamines. This method, however, restricts the synthesis to saturated kephalins.



In agreement with Rose (*loc. cit.*), we found Kabashima's method (*Ber.*, 1938, **71**, 76) quite impracticable. This method consists in heating together bromoethylamine picrate and the monosilver salt of the phosphatidic acid (II) the latter being obtained by a Schotten–Baumann acylation of glycerophosphoric acid. We had no success with either stage of the reaction. A somewhat similar method, suggested by the work of Arnold (*Ber.*, 1940, **73**, 87), namely, heating the disilver salt of the phosphatidic acid (II) (made by direct phosphorylation of the diglyceride) with an alcoholic solution of bromoethylamine hydrobromide, gave an authentic specimen of kephalin, but in too low a yield for the method to be of any practical value.

X-*Ray Investigation.*—This was carried out as described in earlier papers (*J.*, 1934, 666; 1936, 1628), pressed layers and rods being used to give long and side spacings respectively. Exposures of one hour each side for the former, and of ½ hour for the latter are adequate.

TABLE I.

X-Ray spacings (A.) *of* (±)-α- *and* β-*kephalins* (1 : 2- *and* 1 : 3-*diacylphosphatidyl-ethanolamines, respectively*).

(±)-α-Kephalins	Long spacing	Side spacings *							
		w	w	vs	m	w			
Dilauroyl	45·2	5·91	4·91	4·15	3·86	3·59			
Dimyristoyl	49·9	5·96	4·94	4·18	3·87	3·6			
Dipalmitoyl	55·3	5·93	4·92	4·16	3·84	3·59			
Distearoyl	60·0	5·88	4·94	4·2	3·86	3·6			
β-Kephalins		s	vs	m	m	w	m	m	m
Dilauroyl	35·9	5·65	4·72	4·31	4·17	3·89	3·70	3·55	3·42
Dimyristoyl	40·1	5·65	4·69	4·33	4·20	3·97	3·78	3·60	3·40
Dipalmitoyl	44·3	5·59	4·65	4·30	4·25	3·97	3·79	3·57	3·38
Distearoyl	48·3	5·59	4·64	4·33	4·23	3·89	3·79	3·63	3·38
(−)-α-Kephalin (Baer, Marukas, & Russell, *loc. cit.*)		Side spacings							
Dimyristoyl	5·84	5·12	4·69	4·09	3·82	2·99	2·42	2·25	—	1·97
	(0·3)	(0·3)	(0·5)	(1·0)	(0·7)	(0·2)	(0·1)	(0·1)	—	(0·3)
Dipalmitoyl	—	—	4·63	4·13	3·74	3·15	2·8	2·48	2·23	1·82
	—	—	(0·4)	(1·0)	(0·4)	(0·4)	(0·1)	(0·3)	(0·3)	(0·1)
Distearoyl	—	—	4·52	4·12	3·81	3·17	2·24	1·98	—	1·72
	—	—	(0·3)	(1·0)	(0·5)	(0·1)	(0·1)	(0·3)	—	(0·1)

Numbers in parentheses denote estimated intensity of lines.
* s = Strong, vs = very strong, m = moderate, w = weak.

The long spacings, plotted against the number of carbon atoms in the fatty acids, fall accurately on two widely separated straight lines, which give intercepts for no. of C = 0 of $\simeq$ 10 and 15 A. The data agree with an arrangement of double molecules lying at angles of $\simeq$ 73° 20′ (α) and 55° 5′ (β) across the reflecting planes (the angle between the zig-zag carbon atoms of

chains being assumed to be 110°). The side spacings readily distinguish between the α- and β-isomers (see Plate facing p. 2666, Figs. 13 and 14). As would be expected for a homologous series, the spacings and intensities for members of each group are closely similar. These and the long spacings should identify the kephalins with reasonable certainty.

In Table I, we also give, for comparison, spacings calculated from the results of Baer, Marukas, and Russell (*loc. cit.*) for three synthetic (−)-α-kephalins. These are characterised by three strong lines of approximately 4·6, 4·1, and 3·8 A. (the strong shorter spacings are second orders of these). It is difficult to say how far the stereochemical difference affects the crystallographic structure in these compounds, but it is of interest that the 4·1 and 3·8 spacings are very close to our strongest spacings for the (±)-α-kephalin, and that the 4·6 spacing is also very close to the strongest line of our β-kephalin. Whilst these facts are barely sufficient to warrant the deduction that β-kephalin is present in the above compounds, this possibility cannot be overlooked with all synthetic α-kephalins, owing to the facile transformation of 1 : 2-diglycerides, the starting material, into 1 : 3-diglycerides.

Experimental.

1 : 3-*Diglycerides.*—These were prepared by the acid chloride method (Malkin, Shurbagy, and Meara, *J.*, 1937, 1409); we do not recommend the method of direct acylation of glycerol used by Rose (*loc. cit.*), which we find leads to low-melting products containing triglycerides.

1 : 2-*Diglycerides.*—These were prepared as described by Howe and Malkin (preceding paper).

2′-*Hydroxyethylphthalimide* (Rose, *loc. cit.*).—28 G. of freshly distilled ethanolamine were added to 59·2 g. of phthalic anhydride. When the heat of reaction had subsided, the mixture was heated at 150° for 30 minutes, and after cooling to 90° it was poured into 800 c.c. of water. The crystalline product was filtered off on cooling, and recrystallised from water; it had m. p. 130·5° (Rose gives 126—127°).

Solvents and Reagents.—The chloroform used was freed from alcohol with concentrated sulphuric acid, dried ($CaCl_2$; P_2O_5), and distilled, shortly before use. Pyridine was dried (KOH) and fractionated. Phosphorus oxychloride was always fractionated before use. The fatty acids used were Kahlbaum's "K" or highly purified acids, kindly supplied by Messrs. Price's (Bromborough) Ltd. Where necessary, these were purified by fractionation of the ethyl esters.

α- *and β-Kephalins.*—These were made essentially by the same method, except that, following Hunter *et al.* (*loc. cit.*), 2 mol. proportions of 2′-hydroxyethylphthalimide were used for β-kephalins. This method is described in detail only for (±)-α-dimyristoylkephalin; details should be followed closely. Particulars of differences in the amounts of solvent used in individual cases are given in Table II, which gives also yields and m. p.s.

Table II.

Kephalin derivative	Diglyceride dissolved in c.c. of $CHCl_3$	Glycol monomethyl ether, c.c.	Yield, %, based on diglyceride	M. p.	Recorded m. p.
β-Dilauroyl-	50	100	52	208°	—
β-Dimyristoyl-	50	100	47	207	173—174° [1]
β-Dipalmitoyl-	70	200	57	206	192—193, 195—198 [2]
β-Distearoyl-	120	400	76	198	—
(±)-α-Dilauroyl-	50	100	55	210	
(±)-α-Dimyristoyl-	50	100	74	207 [3]	
(±)-α-Dipalmitoyl-	70	200	72	198 [3]	
(±)-α-Distearoyl- ...	120	400	80	196 [3]	

[1] Hunter *et al.* (*loc. cit.*). [2] Rose (*loc. cit.*). [3] Baer, Marukas, and Russell (*loc. cit.*) find all three (−)-α-kephalins to melt in the neighbourhood of 175°.

(±)-α-*Dimyristoylkephalin.* In a 250-c.c. three-necked flask, fitted with a mercury-sealed, mechanically driven Hershberg stirrer, dropping-funnel, and calcium chloride tube (all apparatus previously oven-dried) were placed 10 c.c. of chloroform (alcohol-free; freshly distilled) and 1·535 g. (0·01 mole) of phosphorus oxychloride. The flask was surrounded by an ice-bath and 4·5 c.c. of dry, distilled pyridine were added dropwise to the mixture with vigorous stirring. When all the pyridine had been added, the flask was surrounded by a bath kept at 10—15°, and 5·12 g. of αβ-dimyristin (0·01 mole), dissolved in 50 c.c. of alcohol-free chloroform and 0·5 c.c. of dry pyridine, were added dropwise to the vigorously stirred mixture during 1 hour. The mixture was then stirred for 30 minutes with the bath at 25° and for a further 30 minutes with the bath at 45°.

The bath-temperature was then reduced to 10—15° and 1·91 g. (0·01 mole) of 2′-hydroxyethylphthalimide, dissolved in 70 c.c. of alcohol-free chloroform, were added to the vigorously stirred mixture during one hour. The mixture was then stirred for 30 minutes with the bath at 30°, followed by a further 30 minutes with the bath at 40°. The bath-temperature was then reduced to 10—15° and a few drops of water (*ca.* 0·2 c.c.) were added to the reaction mixture, which was then stirred for 30 minutes. The solvent was then removed under reduced pressure, by use of a water-pump and, finally, a mechanical vacuum pump and a temperature of <40°. (It is particularly important to remove all solvent and so avoid troublesome emulsions.)

The residue was triturated with N-hydrochloric acid at 0—10° and filtered, the precipitate being well washed with cold water (<15°) until free from mineral acid. The precipitate (dried on filter) was dissolved in 100 c.c. of neutral glycol monomethyl ether, a mechanical stirrer and a temperature of <40° being used. When dissolution was complete, 20 c.c. of 0·5N-sodium hydroxide solution were added dropwise to the vigorously stirred mixture, the addition taking about 1 hour. When the addition was complete, 1 g. (0·01 mole) of 50% w/w hydrazine hydrate solution was added to the mechanically stirred mixture, the temperature of which was gradually raised until dissolution was complete (the solution usually contains a small amount of suspended material, which is insoluble until the temperature is raised). Thereafter, the mixture was gently refluxed for 1 hour and then kept overnight. The precipitated material was filtered off and washed with a little neutral glycol monomethyl ether. Further impurities were removed by three extractions with 100 c.c. of boiling ether and finally with 200 c.c. of boiling ether; the yield was 4·7 g., and the m. p. 207° (74% based on 1 : 2-dimyristin).

α- and β-Kephalins may be crystallised from alcohol, but for *X*-ray work slow crystallisation from tetrahydrofuran is preferable. On crystallisation from alcohol on a microscope slide, between crossed nicols, brilliant dark crossed spherulites are observed. The analytical results were as follows: *β-Dilauroylkephalin* [Found: C, 59·6; H, 10·2; P, 5·2; N, 2·4%; equiv. (titration in EtOH; thymolphthalein), 570. $C_{39}H_{84}O_8NP$ requires C, 60·0; H, 10·05; P, 5·35; N, 2·4%; equiv., 579·7]. *β*-Dimyristoylkephalin (Found: C, 62·3; H, 10·4; P, 4·6; N, 1·9%; equiv., 626. Calc. for $C_{43}H_{92}O_8NP$: C, 62·4; H, 10·4; P, 4·9; N, 2·2%; equiv., 635). *β*-Dipalmitoylkephalin (Found: C, 63·9; H, 10·8; P, 4·2; N, 2·0%; equiv., 684. Calc. for $C_{47}H_{76}O_8NP$: C, 64·25; H, 10·7; P, 4·5; N, 2·0%; equiv., 692). *β-Distearoylkephalin* (Found: C, 65·35; H, 10·7; P, 4·0; N, 1·9%; equiv., 737. $C_{51}H_{92}O_8NP$ requires C, 65·9; H, 11·0; P, 4·15; N, 1·9%; equiv., 748). (±)-*α-Dilauroylkephalin* (Found: C, 59·8; H, 10·05; P, 5·0; N, 2·7%; equiv., 570. $C_{39}H_{84}O_8NP$ requires C, 60·0; H, 10·05; P, 5·35; N, 2·4%; equiv., 580). (±)-*α-Dimyristoylkephalin* (Found: C, 62·2; H, 10·3; P, 4·6; N, 2·5%; equiv., 627. $C_{43}H_{88}O_8NP$ requires C, 62·4; H, 10·4; P, 4·9; N, 2·2%; equiv., 636). (±)-*α-Dipalmitoylkephalin* (Found: C, 64·1; H, 10·55; P, 4·1; N, 2·1%; equiv., 687. $C_{47}H_{76}O_8NP$ requires C, 64·25; H, 10·7; P, 4·5; N, 2·0%; equiv., 692). (±)-*α-Distearoylkephalin* (Found: C, 65·3; H, 10·6; P, 3·85; N, 2·0%; equiv., 741. $C_{51}H_{92}O_8NP$ requires C, 65·9; H, 11·0; P, 4·15; N, 1·9%; equiv., 748).

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593. cyclo*Heptatrienone*, cyclo*Pentadienone, and γ-Pyrone.*

By R. D. BROWN.

Predictions are made of the chemistry of *cyclo*heptatrienone, based on molecular-orbital calculations. The related molecules *cyclo*pentadienone and γ-pyrone are also discussed and in particular the theoretical results are shown to give a complete account of the chemistry of the latter, and the tendency of derivatives of the former to dimerize.

RECENTLY the synthesis of *cyclo*heptatrienone was announced simultaneously from two laboratories (Dauben and Ringold, *J. Amer. Chem. Soc.*, 1951, **73**, 876; Doering and Detert, *ibid.*, p. 876) and speculations were made concerning its electronic structure and chemical properties. In the present paper we communicate the values of various theoretical quantities, calculated by the LCAO molecular-orbital approximation (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, **191**, 39), which may be employed to predict the chemistry of this compound. For comparison the corresponding results for *cyclo*pentadienone and γ-pyrone are also reported. It is also of interest to compare the present results with those for tropolone recently obtained by Dewar (*Nature*, 1950, **166**, 790), which are in good agreement with the known chemistry of this molecule (Doering and Knox, *J. Amer. Chem. Soc.*, 1951, **73**, 828).

In the present calculations we have assumed the following values for Coulomb integrals, α, and resonance integrals, β: $\alpha_O = \alpha_C + 2\beta$; $\beta_{CO} = \sqrt{2}\beta_{CC}$. The overlap integrals have been neglected, and we have not considered any slight perturbations to carbon atoms adjacent to oxygen, since it is not yet certain whether or not these are of significant magnitude. The free valences were computed by assuming $N_{max.} = \sqrt{3}$. The atomic localization energies were calculated in the standard manner (Wheland, *J. Amer. Soc.*, 1942, **64**, 900), overlap being neglected. Their significance and relation to chemical properties has already been considered in detail (Wheland, *loc. cit.*; Brown, *Trans. Faraday Soc.*, 1950, **46**, 146). It will be observed that the parameters employed differ somewhat from those used by Dewar (*loc. cit.*) but are similar to those of Orgel *et al.* (*Trans. Faraday Soc.*, 1951, **47**, 113).

The π-electron densities, *q*, atom localization energies, *A*, and free valences, *F*, for various positions in *cyclo*heptatrienone (I) are listed in Table I. It will be noticed that the charge

densities and atomic localization energies (A_e) both predict electrophilic attack to occur at position 2. Likewise the localization energies (A_r) agree with the free valences in attributing also the highest homolytic reactivity to position 2. On the other hand q and A_n are in disagreement as to the position preferentially undergoing substitution by nucleophilic reagents.† If we consider a plot of π-electron energy against motion of the system along the reaction coordinate (Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw-Hill,

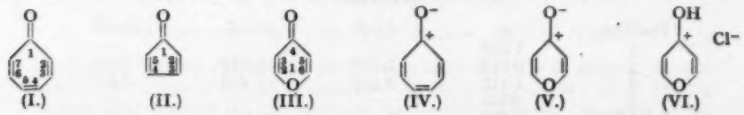
TABLE I.

cyclo*Heptatrienone.*

Position	q	F	$A_e(-\beta)$	$A_r(-\beta)$	$A_n(-\beta)$
O	1·769	—	—	—	—
1	0·771	—	—	—	—
2	0·942	0·494	2·436	2·211	1·987
3	0·884	0·424	2·876	2·508	2·140
4	0·905	0·443	2·644	2·367	2·091

1941, Chap. III), then q indicates the relative positions of the plots for each position in the molecule when the reactants are well separated, while A indicates the relative positions at a stage of the reaction after the reactants have passed through the transition state. Consequently the results for nucleophilic substitution indicate that the curves for positions 2, 3, and 4 cross between these two points, and we cannot be sure which will be lowest at the stage corresponding to the transition state. This perhaps indicates the care that must be exercised in predicting relative reactivities from insufficient theoretical data.

The mobile-bond orders of the *cyclo*heptatrienone bonds, together with the bond localization energies, B (Brown, *Australian J. Sci. Res.*, 1949, **2**, *A*, 564; *J.*, 1950, 3249), for the carbon–carbon ring bonds, are given in Table II. The most interesting point to be deduced from the



(I.) (II.) (III.) (IV.) (V.) (VI.)

mobile orders, p, is that, taken in conjunction with the charge densities of Table I, they reveal that (IV) provides quite a faithful picture of the general electronic structure. Both Dauben and Ringold (*loc. cit.*) and Doering and Detert (*loc. cit.*) consider that the properties of *cyclo*-

TABLE II.

Bond orders and localization energies.

	*cyclo*Heptatrienone		*cyclo*Pentadienone		γ-Pyrone	
Bond	p	$B(-\beta)$	p	$B(-\beta)$	p	$B(-\beta)$
O : 1	0·522	—	0·742	—	—	—
1 : 2	0·530	—	0·289	—	0·565	—
2 : 3	0·709	1·255	0·880	0·549	0·711	1·449
3 : 4	0·600	1·672	0·306	1·086	0·570	—
4 : 5	0·690	1·335	—	—	0·488 *	—

* This value applies to the carbonyl bond, not the ring 4 : 5-bond, which of course is equivalent to the 3 : 4-bond.

heptatrienone so far known are in agreement with such a structure. The bond localization energies indicate that its 2 : 3-bond will be preferentially attacked by, say, ozone, in agreement with the mobile order values, but the product thus formed would be more reactive than the original *cyclo*heptatrienone, so experimental verification of this prediction may prove rather difficult.

For comparison, the π-electron densities, free valences, and atom localization energies of *cyclo*pentadienone are presented in Table III. As with *cyclo*heptatrienone, the data are consistent in predicting electrophilic attack and radical attack at position 2, but the position of highest nucleophilic activity again is uncertain † owing to crossing of the energy curves. It will be noted that the free valences are appreciably greater, and the localization energies smaller,

† We have here ignored the most likely course of reaction, *i.e.*, carbonyl addition involving the 2-position. The possibility of a theoretical treatment of carbonyl reactivity will be considered in a forthcoming publication.

than those for the trienone, which may perhaps be taken as an indication that *cyclo*pentadienone is a more reactive molecule.

TABLE III.

cyclo*Pentadienone.*

Position	q	F	$A_r(-\beta)$	$A_r(-\beta)$	$A_n(-\beta)$
O	1·558	—	—	—	—
1	0·560	—	—	—	—
2	1·082	0·563	1·917	1·601	1·286
3	0·859	0·536	2·290	1·849	1·409

The mobile bond orders and bond localization energies of *cyclo*pentadienone are given in Table II. These point to a high reactivity for the 2 : 3-bond. The bond orders indicate that the most important resonance structure is (II) but the charge densities require an appreciable polarization of the carbonyl bond. A structure analogous to (IV) would, however, not be so appropriate for this molecule as for *cyclo*heptatrienone.

The charges and localization energies for γ-pyrone are listed in Table IV. Both quantities agree in predicting substitution by electrophilic reagents to be most rapid at position 3, and attack by nucleophilic reagents to occur most easily at position 2. The bond orders (Table II) indicate that (V) is the best single representation of the electronic structure of γ-pyrone, and the bond localization energy of the 2 : 3-bond shows that it is probably not so reactive as the mobile order indicates.

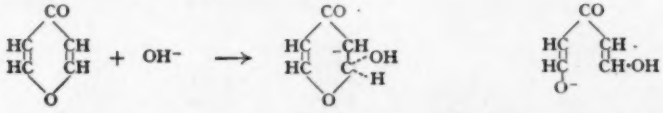
These results are in keeping with the known chemistry of γ-pyrone. The general charge distribution suggests that the oxonium salts which γ-pyrone forms with acids have structures

TABLE IV.

γ-Pyrone.

Position	q	$A_r(-\beta)$	$A_r(-\beta)$	$A_n(-\beta)$
1	1·522	—	—	—
2	0·819	3·017	2·749	2·481
3	1·117	2·193	2·432	2·671
4	0·808	—	—	—
O (of CO)	1·796	—	—	—

such as (VI). The bromination of γ-pyrone giving 3-bromo- and 3 : 5-dibromo-4-pyrone (Feist and Baum, *Ber.*, 1905, **38**, 3562) demonstrates the superior electrophilic reactivity of the 3-position. The high nucleophilic activity of position 2 explains the instability of γ-pyrone in alkaline solution. The resultant ring opening may be formulated as being initiated by attack by nucleophilic reagents at position 2 :



Finally we may enquire into the possibility of *cyclo*heptatrienone undergoing diene-addition reactions. The Diels–Alder properties of hydrocarbon systems have been discussed in some detail in terms of para-localization energies, P, which represent approximations to the variable portion of the activation energy for the diene reaction, by Brown (*J.*, 1950, 691, 2730; 1951, 1612). Para-localization energies for some pairs of positions in *cyclo*heptatrienone and *cyclo*pentadienone are given in Table V, together with corresponding data for fulvene (VII). The para-localization energy for positions 2 : 5 in fulvene lies between the values for the most reactive positions in naphthalene and in anthracene respectively, in keeping with the experimental fact that fulvenes add maleic anhydride fairly readily (*e.g.*, Norton, *Chem. Reviews*, 1942, **31**, 319). The value of P for the corresponding positions in *cyclo*pentadienone is appreciably smaller, indicating much greater Diels–Alder reactivity. It is not surprising therefore that the simpler *cyclo*pentadienones dimerize extremely readily, the only reasonably stable compounds being those in which both 2- and 5-positions carry phenyl groups (Norton, *loc. cit.*). It can be shown (Brown, unpublished work) that the effect of such substituents is to increase significantly the localization energy; at the same time the dienophilic activity of the molecule is probably decreased owing to steric

(VII.)

hindrance by the substituents. In spite of this, tetraphenyl*cyclo*pentadienone undergoes the diene reaction with maleic anhydride (Dilthey, Schommer, and Trosken, *Ber.*, 1933, **66**, *B*, 1627; Allen and Sheps, *Canad. J. Res.*, 1934, **11**, 171). These observations confirm the high diene activity of *cyclo*pentadienone itself.

TABLE V.

Para-localization energies.

Compound	Positions	$P(-\beta)$	Compound	Positions	$P(-\beta)$
Fulvene	2 : 5	3·47	*cyclo*Pentatrienone	2 : 5	3·79
				2 : 7	3·81
*cyclo*Pentadienone	2 : 5	3·04		3 : 6	4·33

In contrast, the smallest localization energy for *cyclo*heptatrienone (for the 2 : 5-positions) is somewhat greater than that for 1 : 4-addition to naphthalene, so it may be predicted that *cyclo*heptatrienone will not be prone to dimerization by a Diels–Alder mechanism, even if it proves to be an effective dienophil.

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594. *The β-Phenylserine Series. Part I.*

By ERNST D. BERGMANN, H. BENDAS, and W. TAUB.

Esters of glycine condense with *p*-nitrobenzaldehyde in alcohol, to give esters of *N*-*p*-nitrobenzylidene-*threo*-β-*p*-nitrophenylserine (II). Hydrochloric acid hydrolyses the products to β-*p*-nitrophenylserine ester hydrochlorides. A number of aromatic aldehydes (but not all) undergo analogous condensations. Lithium aluminium hydride reduces the phenylserine esters to the corresponding alcohols.

Of the esters of other amino-acids investigated, only alanine esters behave analogously. From optically active alanine methyl ester, optically active condensation products are obtained.

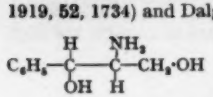
Some experiments expected to elucidate the configuration of β-phenylserine are recorded.

THE most puzzling aspect of the recently established structure of chloramphenicol ("Chloromycetin") is the problem of the biogenesis of the compound: not only is the presence of a nitro-group and of the dichloroacetyl radical unusual, but also the biological synthesis of the corresponding alcohol (I) skeleton appears obscure. If one assumes that it is derived from the substituted β-phenylserine (the reverse reaction is known in the oxidation of chloramphenicol to *p*-nitrophenylserine; Smith and Worrel, *Arch. Biochem.*, 1950, **28**, 232), the problem is reduced to that of the biosynthesis of β-phenylserines. It will be recalled that the alcohols corresponding to alanine occur in Nature (Jacobs and Craig, *Science*, 1935, **82**, 16).

In analogy with the formation of serine from formaldehyde and glycine, one would expect a substituted β-phenylserine to be formed from a substituted benzaldehyde and glycine. Reactions of this type are not new in principle. Fifty years ago, Erlenmeyer (*Annalen*, 1899, **307**, 84; cf. *idem*, *ibid.*, 1904, **337**, 222; Erlenmeyer and Fruestueck, *ibid.*, 1895, **284**, 36) described the formation of β-phenylserine from benzaldehyde and glycine under the influence of strong alkali, its *N*-benzylidene derivative being the final product.* Erlenmeyer also stated that other aldehydes (except *o*-anisaldehyde) did not react analogously—this

* Erlenmeyer's discovery has been obscured by the uncertainty introduced into the field by the subsequent investigations of Forster and Rao (*J.*, 1926, 1943), Oesterlin (*Centralbl.*, 1929, II, 1398), and Fourneau and Billeter (*Bull. Soc. chim.*, 1940, **7**, 593). However, the link recently established between β-phenylserine and chloramphenicol (see below) proves not only the configuration, but also the constitution, of Erlenmeyer's amino-acid.

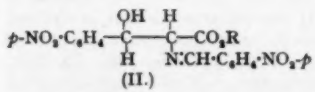
has now been confirmed in experiments with anisaldehyde. Rosenmund and Dornsaft (*Ber.*, **1919**, **52**, 1734) and Dalgliesh (*J.*, 1949, **90**; cf. Dalgliesh and Mann, *J.*, 1947, 658) extended the scope of the reaction somewhat, using sodium in ether in order to achieve the condensation of aromatic aldehydes and glycine esters; they applied the reaction to anisaldehyde, *p*-carbethoxyoxybenzaldehyde, *O*-carbethoxyvanillin, *OO*-dicarbethoxyprotocatechualdehyde, and *p*-nitrobenzaldehyde. The configuration of Erlenmeyer's β-phenylserine is identical with that of chloramphenicol (*threo*); this has been proved by Carrara and Weitnauer (*Gazzetta*, 1949, **79**, 856), by Vogler (*Helv. Chim. Acta*, 1950, **33**, 2111), by experiments already published from this laboratory (Bendas and E. Bergmann, *Bull. Res. Council Israel*, 1951, **1**, 131), and by others now reported through lithium aluminium hydride reduction of the ester to that alcohol (I) which on nitration gives chloramphenicol. This appears to strengthen the thesis that this condensation reaction represents the "natural" synthesis of the chloramphenicol skeleton, although, of course, the agent used for the condensation is not biogenic. Shaw and Fox (quoted by Vogler, *loc. cit.*) reported recently the isolation of the *erythro*-form of β-phenylserine by a modification of Erlenmeyer's method (cf. also Elphimoff-Felkin and Felkin, *Compt. rend.*, 1951, **232**, 241).



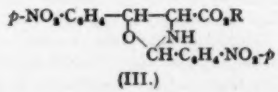
(I.)

The rather unexpected observation (E. Bergmann, Genas, and Bendas, *Compt. rend.*, 1950, **231**, 361) is, therefore, of interest, that *p*-nitrobenzaldehyde and glycine methyl (or ethyl) ester condense easily, at room temperature and without a catalyst, in methanolic solution to give the *N*-*p*-nitrobenzylidene derivative (II) (m. p. 144°) of the corresponding *p*-nitrophenylserine ester, which crystallises partly from the reaction mixture. If excess of alcoholic hydrochloric acid and ether is added to the reaction mixture or to the mother-liquor from (II), the hydrochloride of the *p*-nitrophenylserine ester is precipitated. The condensation is fairly fast; no difference in yield of the hydrochloride was observed for the mixture of 2 mols. of aldehyde (*m*-nitrobenzaldehyde and glycine ethyl ester were used in these experiments) and 1 mol. of ester after 24, 64, or 110 hours. The yield was 52%; it was increased to 74% if the molar ratio aldehyde : ester was changed to 1 : 1; this points to an equilibrium being reached in the condensation under the conditions employed.

Dalgliesh (*loc. cit.*) observed in the sodium condensation of glycine methyl ester and *p*-nitrobenzaldehyde two products of the composition of (II), melting at 85° and 139°, respectively. He ascribed formula (II) to the lower-melting, less stable product, and the oxazolidine formula (III) to the higher-melting stable isomer. This assignment has to be reversed; the higher-melting substance (m. p. 144°) is (II). This has been proved by infra-red analysis, which revealed the presence of a C=N bond (absorption at 1656 cm.$^{-1}$), whilst the oxazolidines have no absorption band at this wave-length and are characterized by a band triplet in the region of 1100—1200 cm.$^{-1}$ (E. Bergmann, Zimkin, and Pinchas, *Rec. Trav. chim.*, in the press; Daasch and Hanninen, *J. Amer. Chem. Soc.*, 1950, **72**, 3673). Indeed, experiments to be reported elsewhere (E. Bergmann, Zimkin, and Pinchas, *loc. cit.*) have shown that the stable products formed from amino-alcohols and aromatic aldehydes are usually Schiff's bases and not oxazolidines, the conjugation between the C=N double bond and the aromatic nucleus stabilizing the open form.



(II.)



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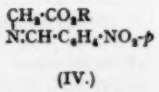


(IV.)

The configuration of (II) and of the corresponding *p*-nitrophenylserine is the same (*threo*) as in Erlenmeyer's β-phenylserine and in chloramphenicol, as reduction with lithium aluminium hydride led to the racemic form of *threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol (Rebstock, Crookes, Controulis, and Bartz, *J. Amer. Chem. Soc.*, 1949, **71**, 2458). The simple condensation between *p*-nitrobenzaldehyde and glycine ester gives, therefore, not only the correct structure, but also the correct configuration of the chloramphenicol molecule. This reduction was made possible by the observation (Felkin, *Compt. rend.*, 1950, **230**, 304) that lithium aluminium hydride reduces ester groups faster than the nitro-group. However, the yields leave much to be desired, and further experiments are in hand.

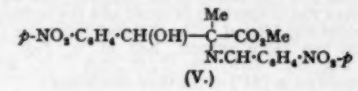
The non-catalysed condensation of an amino-acid ester with *p*-nitrobenzaldehyde is a novel reaction in which a hydrogen atom on the α-carbon atom is involved. It recalls, therefore, to some extent the observation by Haenel (*Naturwiss.*, 1950, **37**, 91) that ethyl alkylidenesuccinates

condense with aldehydes and ketones without catalyst, simply on prolonged heating at elevated temperature.

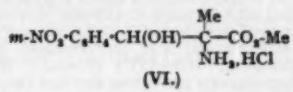
In the normal condensation of aromatic aldehydes with amino-acids, the azlactone synthesis, in which the amino-acid is employed in its *N*-acylated form and which requires acetic anhydride as condensing agent, condensation does take place at the methylene group but is accompanied by the elimination of water. In aqueous-alkaline solution, however, only the amino-group of the amino-acid anion reacts with aromatic aldehydes, and salts of *N*-arylideneamino-acids are obtained (M. Bergmann, Ensslin, and Zervas, *Ber.*, 1925, **58**, 1034). It is assumed that also in the present case one molecule of *p*-nitrobenzaldehyde reacts first with the amino-group of glycine ester; in the *N*-*p*-nitrobenzylidene derivative (IV), the methylene group is activated by the two adjacent double bonds in the same way as in ethyl acetoacetate or malonate and thus enabled to undergo the aldol-type condensation with a second molecule of the aldehyde. This hypothesis is supported by the observation that neither sarcosine methyl ester nor *NN*-dimethylglycine methyl ester condenses with *p*-nitrobenzaldehyde in methanol.

It appeared interesting to study systematically the scope of the new reaction. The following aromatic aldehydes gave a positive response: * *p*-, *o*-, and *m*-nitro-, *p*-cyano-, *p*-carbethoxyoxy-, *p*-hydroxy-, and 2 : 6-dichloro-benzaldehyde, and furfuraldehyde; but in the last case resinification occurred. The following aldehydes proved refractory: *p*-dimethylamino-, 2 : 4-dinitro-, *p*-benzyloxy-, and 3-nitro-4-hydroxy-benzaldehyde, anisaldehyde, and 2-formylthiophen. Also, benzil could not be induced to react with glycine ethyl ester. In some cases, the products corresponding to (II) were precipitated; in others, addition of alcoholic hydrochloric acid and ether led to hydrolysis of the C=N bond and precipitation of the hydrochloride of the expected substituted β-phenylserine ester. Of the amino-acid esters, those of β-phenylalanine, glutamic, and aspartic acid could not be induced to react. Alanine methyl ester, on the other hand, reacted with *p*-nitrobenzaldehyde (but not with benzaldehyde or anisaldehyde) as did glycine esters, giving a crystalline product (V) corresponding to (II). Its ester group could be hydrolysed without affecting the C=N bond. Infra-red analysis of the free acid has shown the presence of a free hydroxyl group (3400 and 1104 cm.$^{-1}$, the latter characteristic of the secondary hydroxyl group), and a broad band in the C=N absorption region, which is probably composed of the C=N band proper and the absorption of the C=O group of the carboxyl (1714 cm.$^{-1}$). In addition, a weak band at 1164 cm.$^{-1}$ was observed, most probably due to the *iso*propyl skeleton, but no trace of the characteristic oxazolidine absorption was detected.

No attempt has been made, so far, to prove the configuration of the new substituted β-phenylserines; it can be assumed that their configuration will prove to be identical with that of the parent substance and of the *p*-nitro-compound. In this respect, it was of interest to investigate whether an optically active amino-acid would given an active derivative or suffer racemisation during condensation. Optically activo alanine methyl ester gave a lævorotatory product (V) with *p*-, and a dextrorotatory hydrochloride (VI) with *m*-nitrobenzaldehyde.



(V.)



(VI.)

The biological activities of the newly synthesised phenylserines, of the corresponding alcohols, and of some of their derivatives, will be described elsewhere; Buu-Hoï, Hoán, Jacquignon, and Khoï (*J.*, 1950, 2766), Bambas, Troutman, and Long (*J. Amer. Chem. Soc.*, 1950, **72**, 4445), and Dann, Ulrich, and Moeller (*Z. Naturforsch.*, 1950, **5***b*, 446) have reported recently that the halogen analogues of the natural chloramphenicol (halogen instead of nitro) have a considerable activity against *Escheria coli*, *Staphylococcus aureus*, and *Bacillus paratyphosus*.

The *N*-dichloroacetyl derivatives of β-phenylserine and β-*p*-nitrophenylserine have been prepared by Billet (*Compt. rend.*, 1950, **231**, 293) and Woolley (*J. Biol. Chem.*, 1950, **185**, 293); in view of the possibility that the dichloroacetylation attacks the hydroxyl, and not the amino-group, their infra-red spectra have been studied (in paraffin oil). These prove that the substances are indeed the *N*-acyl derivatives (for a detailed discussion of the spectra see the Experimental section): the absorption at 2585 cm.$^{-1}$ (β-phenylserine derivative) and 2530 cm.$^{-1}$ (nitro-compound) is characteristic of the acylamide group in *N*-acylamido-acids.

Some unsuccessful attempts may be briefly recorded, both to elucidate the configuration of β-phenylserine and its *p*-nitro-derivative, and to obtain their (*erythro*-)-

* Ethyl pyruvate gave a vigorous reaction, but no definite product could be isolated.

enantiomers, following the work of Elliott (*Nature*, 1948, **162**, 657; Attenburrow, Elliott, and Penny, *J.*, 1948, 310) and of Pfister, Robinson, Shabica, and Tishler (*J. Amer. Chem. Soc.*, 1949, **71**, 1101) in the threonine series (cf. Weijlard, Pfister, Swanezy, Robinson, and Tishler, *ibid.*, 1951, **73**, 1216). In accordance with Vogler's results (*loc. cit.*), it was found impossible, however, to prepare an oxazoline derivative. The esters of the two acids did not react with ethyl benzimidate in boiling dichloro-, tetrachloro-, or dibromo-ethane (Elliott, *J.*, 1949, 589; Johnson and Schubert, *J. Amer. Chem. Soc.*, 1950, **72**, 2187). Also, the cyclisation of *N*-benzoyl-β-phenylserine ester, according to Valco's method (U.S.P. 2,416,552) failed: in boiling *iso*propylbenzene no reaction occurred, in higher-boiling solvents resinification took place. Equally, no definite derivatives were obtained when the hydrochloride of phenylserine methyl or of *m*-nitrophenylserine ethyl ester was heated with urea (Close, *J. Org. Chem.*, 1950, **15**, 1131).

Treatment of *N*-benzoyl-β-phenylserine methyl ester with thionyl chloride gave the desired methyl α-benzamido-β-chloro-β-phenylpropionate; its treatment with silver acetate (Johnson and Schubert, *loc. cit.*; McCasland, Clark, and Carter, *J. Amer. Chem. Soc.*, 1949, **71**, 637) did not lead to any definite products, although silver chloride was formed. In general, only *threo*-compounds disclose active chlorine in this reaction, but the intractability of the product renders any conclusion as to configuration doubtful.

Experimental.

(M. p.s are uncorrected.)

β-Phenylserine was prepared according to G.P. 632,424 (Ges. fuer Kohlentechnik) in 69% yield. Recrystallisation from 10 parts of 50% alcohol is the best means of purifying it, the m. p. being 198—203° (Carrara and Weitnauer, *loc. cit.*, give 194—195°). The hydrochloride has m. p. 164—166° (decomp.).

A suspension of phenylserine (100 g.) in anhydrous alcohol (300 c.c.) was treated with gaseous hydrogen chloride until a clear solution resulted. The solvent was distilled off *in vacuo* and the crystalline ethyl ester hydrochloride washed with ice-cold alcohol and recrystallised from the same solvent (yield, 100—110 g., 75—77%); it had m. p. 164—165° (decomp.). To an ice-cold solution of the hydrochloride (50 g.) in water (100 c.c.), a cold solution of anhydrous potassium carbonate (50 g.) in water (50 c.c.) was gradually added, with cooling. The free ethyl ester crystallised at once; it was filtered, dried, and recrystallised from light petroleum (yield, 25—30 g., 60—66%; m. p. 82—84°).

The methyl ester hydrochloride, prepared analogously, had m. p. 161° (decomp.), and the free ester m. p. 62° (from light petroleum).

The m. p., given in the abstract (*Chem. Abs.*, 1950, **44**, 7268) of Carrara and Weitnauer's paper (*loc. cit.*) for the esters are those of the hydrochlorides.

threo-3-*Acetoxy*-2-*amino*-1-*phenylpropyl Acetate*.—To lithium aluminium hydride (6 g.) in dioxan (200 c.c.) was added slowly, with vigorous stirring at 100°, a solution of β-phenylserine ethyl ester (12·2 g.) in dioxan (30 c.c.). Water was added to destroy the excess of hydride, and the solid was filtered off and extracted four times with boiling alcohol. The dioxan filtrate and the alcoholic extracts were combined and evaporated, and acetic anhydride (20 c.c.) was added to the residue. The clear solution which resulted after 30 minutes at room temperature was evaporated *in vacuo* and the residue triturated with warm anhydrous alcohol. The mass was cooled and filtered. The diacetyl derivative (9 g.), when triturated with alcohol and recrystallised from the same solvent, had m. p. 165° (lit., 168—169°; *erythro*-form, 110—111°) (Found: N, 5·6, 5·7. Calc. for $C_{13}H_{17}O_4N$: N, 5·6%). The corresponding triacetyl derivative also had the correct m. p. (84°) of the *threo*-compound.

N-p-*Nitrobenzylidene*-β-p-*nitrophenylserine Ethyl Ester*.—When glycine ethyl ester (4 g.) and *p*-nitrobenzaldehyde (12 g.) were dissolved in methanol (30 c.c.) by brief heating, an intensely yellow solution resulted which soon began to deposit crystals of this *ester* which, crystallised from methanol, had m. p. 144° (Found: N, 10·7, 11·0. $C_{18}H_{17}O_7N_3$ requires N, 10·9%).

β-p-*Nitrophenylserine Ethyl Ester Hydrochloride*.—The reaction mixture, prepared as above, or the mother-liquor from the crystals of m. p. 144°, when treated with concentrated alcoholic hydrochloric acid and an excess of ether, gave a thick precipitate. Recrystallisation from butyl alcohol gave the salt, m. p. 189° (decomp.) (Found: N, 9·8. Calc. for $C_{11}H_{15}O_5N_2Cl$: N, 9·6%).

β-p-*Nitrophenylserine Methyl Ester Hydrochloride*.—From glycine methyl ester (4 g.) and *p*-nitrobenzaldehyde (13 g.), dissolved in methanol and kept at room temperature for 6 hours, the ester (III; R = Me) (7 g.) was obtained by cooling at 0°. Treatment of the total reaction mixture with an excess of methyl-alcoholic hydrochloric acid (2 mols. per mol. of ester) and double the volume of ether, gave the *hydrochloride* (6·3 g., 50%), m. p. 183° (decomp.) (from methanol–ether) (Found: N, 10·1. $C_{10}H_{13}O_5N_2Cl$ requires N, 10·1%).

β-m-*Nitrophenylserine Methyl Ester Hydrochloride*. The condensation product (as III) from glycine methyl ester (2·3 g.) and *m*-nitrobenzaldehyde (7·6 g.) in methanol, separated as a viscous oil. Both the oil and the supernatant liquid, when treated with methanolic hydrochloric acid and ether, gave the same *hydrochloride*, which after recrystallisation from butyl alcohol, had m. p. 131° (Found: N, 10·0, 10·2; Cl, 12·4, 12·4. $C_{10}H_{13}O_5N_2Cl$ requires N, 10·1; Cl, 12·7%).

The reaction mixture from glycine ethyl ester (5·2 g.) and *m*-nitrobenzaldehyde (15 g.) in ethyl alcohol (50 c.c.) was treated with alcoholic hydrochloric acid (9 c.c.) and ether (200 c.c.) and cooled at 0°. The yield of *β-m-nitrophenylserine* ethyl ester hydrochloride was 7·4 g. after 24 hours at room temperature, and 7·0 and 7·2 g. after 64 and 110 hours, respectively. When 10·4 g. of ester and 100 c.c. of ethyl alcohol were used, the yield was 10·7 g. The m. p. was 180—184° (decomp.).

β-m-Nitrophenylserine.—To *m*-nitrophenylserine ethyl ester hydrochloride (10·9 g.), wetted with a few drops of methanol, N-sodium hydroxide (75 c.c.) was added. After 1 hour at room temperature, the mixture was neutralised with N-hydrochloric acid (37·5 c.c.). Immediately, needles began to separate. *β-m-Nitrophenylserine* crystallised from water and had m. p. 203° (decomp.) (6·5 g.) (Found: N, 12·7. $C_9H_{10}O_5N_2$ requires N, 12·4%).

N-*o-Nitrobenzylidene-β-o-nitrophenylserine Ethyl Ester.*—This ester crystallised spontaneously from the reaction mixture of glycine ethyl ester (5·2 g.) and *o*-nitrobenzaldehyde (15 g.); the mother-liquor, on treatment with hydrochloric acid, gave very little precipitate. The *ester* separated from propanol in prisms, m. p. 160° (Found: N, 10·7. $C_{18}H_{17}O_7N_3$ requires N, 10·9%).

When the total reaction product was treated directly with hydrogen chloride (1·85 g.) in alcohol (8·7 c.c.) and an excess of ether, *β-o-nitrophenylserine ethyl ester hydrochloride* (3·6 g.) crystallised. Recrystallised from *iso*propyl alcohol, it had m. p. 141° (Found: N, 9·8. $C_{11}H_{13}O_5N_2Cl$ requires N, 9·6%).

β-Phenylserine methyl ester hydrochloride was obtained analogously in small yield from glycine methyl ester and benzaldehyde and had m. p. 161° (decomp.) (from butyl alcohol) (Found: N, 6·2; Cl, 14·8, 14·9. Calc. for $C_{10}H_{14}O_3NCl$: N, 6·1; Cl, 15·1%).

N-(2 : 6-*Dichlorobenzylidene*)-*β*-2 : 6-*dichlorophenylserine Methyl Ester.*—A solution of glycine methyl ester (2·3 g.) and 2 : 6-dichlorobenzaldehyde (8·8 g.) in alcohol was kept at room temperature for 3 days and cooled at 0°. The condensation *product* (1·7 g.) separated and after recrystallisation from butyl acetate had m. p. 128° (Found: N, 3·5, 3·6; Cl, 35·7, 35·9. $C_{17}H_{13}O_3NCl_4$ requires N, 3·3; Cl, 33·8%).

Treatment of the alcoholic mother-liquor with hydrogen chloride and ether gave *β*-2 : 6-*dichlorophenylserine methyl ester hydrochloride*, prisms (from butanol), m. p. 198° (1·4 g.) (Found: C, 40·1; H, 4·2; Cl, 35·4. $C_{10}H_{11}O_3NCl_3$ requires C, 40·0; H, 4·0; Cl, 35·3%).

N-*p-Cyanobenzylidene-β-p-cyanophenylserine Methyl Ester.*—The methanolic solution of glycine methyl ester (0·1 g.) and *p*-cyanobenzaldehyde (0·2 g.) (E. Bergmann and Pinchas, *J. Org. Chem.*, 1950, **15**, 1184, have stressed the similarity in electronic structure and chemical reactivity of *p*-nitro- and *p*-cyano-benzaldehyde) yielded crystals after a few hours. Crystallised from butyl alcohol, this *benzylidene* derivative had m. p. 278° (decomp.) (Found: C, 68·4; H, 4·6; N, 12·8. $C_{19}H_{14}O_3N_3$ requires C, 68·5; H, 4·5; N, 12·6%).

4-Hydroxy-3-nitrobenzaldehyde (cf. Paal, *Ber.*, 1895, **28**, 2407).—A mixture of *p*-hydroxybenzaldehyde (20 g.), acetic acid (80 c.c.), and nitric acid (*d* 1·42; 11 c.c.) was very cautiously heated to 40°. At this point, a violent reaction set in, which raised the temperature to 80°. The mass was cooled rapidly with running water, and water (80 c.c.) was added. After 12 hours, the crystals of 4-hydroxy-3-nitrobenzaldehyde were collected and recrystallised from *iso*propyl alcohol (yield, 13·5 g., 50%); they had m. p. 141—142°.

Glycine methyl ester (3 g.) and this aldehyde (9·9 g.) in methanol gave an orange-red solution which after 4 days at room temperature was treated with hydrochloric acid in the customary manner. A resinous product separated at 0°, which was triturated with methanol and recrystallised from *iso*propyl alcohol as yellow prisms, m. p. 222°, which were chlorine-free. This *substance* had approximately the same composition as the starting material and was not further investigated (Found: C, 50·8; H, 3·3; N, 8·2. $C_9H_8O_4N$ requires C, 50·3; H, 3·0; N, 8·4%).

β-p-Carbethoxyoxyphenylserine Ethyl Ester Hydrochloride.—A mixture of glycine ethyl ester (3·1 g.) and *p*-carbethoxyoxybenzaldehyde (12 g.) (Rosenmund and Dornsaft, *loc. cit.*) (b. p. 172—174°/23 mm.) in alcohol reacted slightly exothermally but gave no precipitate. Addition of alcoholic hydrochloric acid and ether gave the desired *salt* (6·5 g.) which was purified by precipitation from its methanolic solution with anhydrous ether and had m. p. 157° (decomp.) (Found: C, 50·0; H, 6·4; N, 4·5, 4·5. $C_{14}H_{20}O_6NCl$ requires C, 50·4; H, 6·0; N, 4·2%).

β-p-Hydroxyphenylserine Ethyl Ester Hydrochloride.—When *p*-hydroxybenzaldehyde (12 g.) and glycine ethyl ester (5·2 g.) were kept at room temperature in alcohol, no crystalline product separated. Addition of an alcoholic solution of hydrogen chloride (1·85 g.) and ether yielded the *salt* (1·3 g.) which was reprecipitated repeatedly from methanol by addition of anhydrous ether. It melted at 128° (Found: N, 5·5. $C_{11}H_{16}O_4NCl$ requires N, 5·6%).

β-p-Hydroxyphenylserine.—The foregoing ester (1·0 g.) was hydrolysed at room temperature by N-potassium hydroxide (7·5 c.c.); addition of N-hydrochloric acid (3·75 c.c.) precipitated the substituted serine. From a mixture of water and *tert.*-butanol, it crystallised in fine needles, which began to decompose at 197° (Found: N, 7·1. Calc. for $C_9H_{11}O_4N$: N, 7·1%). According to Rosenmund and Dornsaft (*loc. cit.*), the amino-acid discolors at 190° and decomposes gradually when heated to 217°.

Methyl (±)-β-Hydroxy-α-p-nitrobenzylideneamino-β-p-nitrophenylisobutyrate.—When DL-alanine methyl ester (5 g.) and *p*-nitrobenzaldehyde (15 g.) were kept in methanol (50 c.c.) (colour: orange-red), the condensation product (2 g.) was precipitated. A second crop was obtained by evaporation

of the methanolic mother-liquor. The *ester*, recrystallised from methanol or ethyl alcohol, had m. p. 142° (yield, 9 g., 46%) (Found : N, 10·9, 10·9. $C_{16}H_{17}O_7N_3$ requires N, 10·9%). The hot solution in butyl alcohol is rose-coloured.

The methyl ester (1·4 g.) was kept in N-sodium hydroxide for 1 hour at room temperature. The colour changed from violet-brown to yellowish. The *acid* was precipitated by N-hydrochloric acid (4·8 c.c.) and recrystallised from slightly acidified water; it formed long yellowish needles, m. p. 105° (Found : C, 54·5; H, 3·7; N, 10·8. $C_{17}H_{15}O_7N_3$ requires C, 54·7; H, 4·0; N, 11·2%).

Optically Active Methyl β-Hydroxy-α-p-nitrobenzylideneamino-β-p-nitrophenylisobutyrate.—The product from L-alanine methyl ester (0·4 g.) and *p*-nitrobenzaldehyde (1 g.) crystallised spontaneously. From *iso*propyl alcohol, this *ester* formed crystals, m. p. 138—139°, $[\alpha]_D$ −2·2° ± 0·4° (*c*, 2·25 in chloroform) (Found : C, 55·4; H, 4·7; N, 10·6. $C_{18}H_{17}O_7N_3$ requires C, 55·8; H, 4·4; N, 10·9%).

Optically Active Methyl β-Hydroxy-α-m-nitrobenzylideneamino-β-m-nitrophenylisobutyrate Hydrochloride.—L-Alanine methyl ester (1 g.) and *m*-nitrobenzaldehyde (3 g.) in a little methanol were kept at room temperature for 48 hours, and excess of methanolic hydrochloric acid and ether added. Scratching precipitated the *hydrochloride*. It was purified by addition of anhydrous ether to its filtered methanolic solution and had m. p. 144° (decomp.), $[\alpha]_D$ 10·4° ± 2·4° (*c*, 1·25 in acetic acid) (Found : N, 9·5. $C_{11}H_{14}O_4N_2Cl$ requires N, 9·7%).

N-*Dichloroacetyl-β-phenylserine.*—This was obtained according to Billet (*loc. cit.*) but isolated by keeping the reaction product at low temperature for several hours. Crystallised from water containing a little acetic acid, or from toluene, it had m. p. 158° (decomp.) (Billet gives m. p. 170°) (Found : Cl, 23·9, 24·0. Calc. for $C_{11}H_{11}O_4NCl_2$: Cl, 24·3%). The quantity of dichloroacetyl chloride prescribed by Woolley (*loc. cit.*) is too small; one needs 8·1 g. for 9 g. of the amino-acid. The infra-red spectrum revealed the presence of the following bands : (1; sample from water) **3320**, **2585**, **1724**, **1674**, **1536**, **1274**, **1223**, **719** cm.$^{-1}$; (2; sample from toluene) **3320**, **2565**, **1714**, **1672**, **1534**, **1273**, **1224**, **719** cm.$^{-1}$. That the substance is the *N*-dichloroacetyl derivative is shown by the bands : **3320** (hydroxyl, both alcoholic and of the carboxyl group), **2585** (acylamido-acid) (Randall *et al.*, " Infra-red Determination of Organic Substances," New York, 1949, pp. 134, 135, 141), **1724** (C=O of the carboxyl group), **1674** (C=O of the amide group), **1536** (NH in amides), **1274** (secondary hydroxyl group) (Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397), **1223** (C–N in =C–N–C) (Randall *et al.*, *op. cit.*, p. 127, show, *e.g.*, for α-acetamido-ββ-dimethylacrylic acid a band at 1230 cm.$^{-1}$), and **719** (CCl_2).

N-*Dichloroacetyl-β-p-nitrophenylserine.*—Obtained analogously and crystallised from water, this formed faintly yellowish needles, m. p. 176° (Found : N, 8·4. Calc. for $C_{11}H_{10}O_6N_2Cl_2$: N, 8·3%). The infra-red spectrum showed that the substance was the *N*-dichloroacetyl compound. **3375** (free alcoholic hydroxyl), **3240** (hydroxyl of the carboxyl group), **2530** (acylamido-acid), **1738** (C=O of the carboxyl group), **1683** (C=O of the amide group), **1609** (phenyl), **1563** (NH in amides), **1521** (substituted phenyl), **1229** (C–N in =C–N–C), **753** (substituted phenyl), **721** (CCl_2).

N-*Benzoyl-β-phenylserine.*—A solution of β-phenylserine (36·2 g.) and sodium hydroxide (8·0 g.) in water (100 c.c.) and a solution of benzoyl chloride (28·0 g.) in benzene (100 c.c.) were stirred together, and sodium hydroxide (8 g.) in water (100 c.c.) was added slowly. Addition of N-sulphuric acid (200 c.c.) precipitated the *benzoyl* derivative. Washed with ether and recrystallised from 30% ethanol, it (45 g., 80%) had m. p. 160—161° (Found : C, 67·4; H, 5·1; N, 5·1. $C_{16}H_{15}O_4N$ requires C, 67·4; H, 5·3; N, 4·9%).

The acid (14·3 g.) and diazomethane (4·0 g.) in ether (150 c.c.) gave the *methyl* ester (13 g., 87%), m. p. 123—124° (from dilute alcohol) (Found : N, 4·8. $C_{17}H_{17}O_4N$ requires N, 4·7%).

In contradistinction to free amino-acids, the *N*-acyl derivatives are smoothly methylated by diazomethane (Herzig and Landsteiner, *Biochem. Z.*, 1920, **105**, 111; cf. Biltz and Paetzold, *Ber.*, 1922, **55**, 1066; Kuhn and Brydowna, *ibid.*, 1937, **70**, 1333).

Methyl α-Benzamido-β-chloro-β-phenylpropionate.—The foregoing product (16 g.) and freshly distilled, ice-cold thionyl chloride (6 c.c.) were kept at room temperature for 2 hours. Ether (150 c.c.) precipitated the *chloro*-compound which, recrystallised from dilute alcohol, had m. p. 133—134° (2·3 g.). From the ethereal mother-liquor, a further 1·2 g. were obtained (Found : N, 4·7; Cl, 10·8. $C_{17}H_{16}O_3NCl$ requires N, 4·4; Cl, 11·0%). The infra-red spectrum (0·0054 g. in 1 c.c. of carbon tetrachloride; cell thickness, 2 mm.) showed the amide-carbonyl band at 1677 cm.$^{-1}$ and the amide-NH band at 3430 cm.$^{-1}$.

The infra-red spectra were measured and interpreted by Dr. S. Pinchas, Optics Department, Weizmann Institute of Science.

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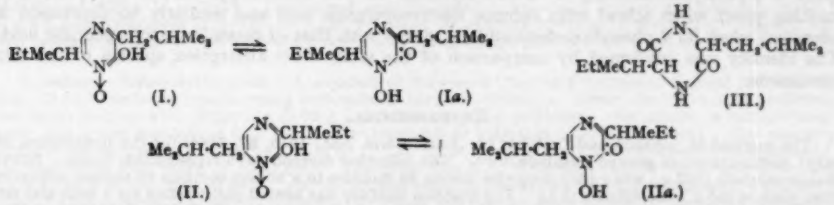
595. *Aspergillic Acid. Part III.* The Synthesis of Racemic Deoxyaspergillic Acid.*

By G. T. Newbold, William Sharp, and F. S. Spring.

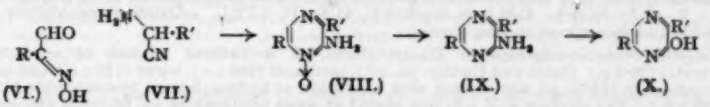
The synthesis of 2-*iso*butyl-5-*sec.*-butyl-3-hydroxypyrazine (IV) is described; it is identical with racemic deoxyaspergillic acid. This synthesis establishes the structure of aspergillic acid as 3-*iso*butyl-6-*sec.*-butyl-2-hydroxypyrazine 1-oxide (I).

Degradative experiments have established that the antibiotic aspergillic acid is either 3-*iso*butyl-6-*sec.*-butyl-2-hydroxypyrazine 1-oxide (I or I*a*) or 6-*iso*butyl-3-*sec.*-butyl-2-hydroxypyrazine 1-oxide (II or II*a*). The nature of the alkyl side chains was established by conversion of the antibiotic into a diketopiperazine (III), hydrolysis of which gave a mixture of leucine and *iso*leucine (Dunn, Gallagher, Newbold, and Spring, *J.*, 1949, S 126; Dunn, Newbold, and Spring, *J.*, 1949, S 131).



Reduction of aspergillic acid with hydrazine gives deoxyaspergillic acid (Dutcher, *J. Biol. Chem.*, 1947, **171**, 321) which according to Dunn, Newbold, and Spring (*loc. cit.*) is either 2-*iso*butyl-5-*sec.*-butyl- (IV) or 5-*iso*butyl-2-*sec.*-butyl-3-hydroxypyrazine (V). Deoxyaspergillic acid is readily racemised when heated with alkali (Dunn, Gallagher, Newbold, and Spring, *loc. cit.*). This paper describes a synthesis of racemic deoxyaspergillic acid and its identification as 2-*iso*butyl-5-*sec.*-butyl-3-hydroxypyrazine (IV). It follows that aspergillic acid is the corresponding oxide (I).

Condensation of an oximinomethyl ketone with an α-amino-nitrile yields a 3 : 5-disubstituted 2-aminopyrazine 1-oxide, reduction of which with sodium dithionite (hydrosulphite) gives a 3 : 5-disubstituted 2-aminopyrazine (Sharp and Spring, *J.*, 1951, 932). The synthesis of a 2 : 5-disubstituted 3-aminopyrazine by a similar method would require the condensation of an α-oximino-aldehyde (VI) with an α-amino-nitrile (VII). A method has been developed for the synthesis of α-oximino-aldehydes, which so far as we are aware have not been previously



described. Treatment of methylglyoxal diethyl acetal (XI; R = Me) (Dakin and Dudley, *J.*, 1914, **105**, 2453) with hydroxylamine gives α-oximinopropaldehyde diethyl acetal (XII; R = Me) from which α-oximinopropaldehyde (VI; R = Me) was obtained in good yield by hydrolysis with acetic acid–sodium acetate solution. α-Oximinopropaldehyde is very similar in solubility and odour to oximinoacetone but it is less stable, extensive decomposition occurring during a few months' storage under normal conditions. In a similar manner *sec.*-butylglyoxal diethyl acetal (XI; R = Bu^s) (Dakin and Dudley, *loc. cit.*) was converted into the oximino-acetal (XII; R = Bu^s) and thence into β-methyl-α-oximino-*n*-valeraldehyde (VI; R = Bu^s).

Reaction of α-oximinopropaldehyde (VI; R = Me) in chloroform solution with α-amino-

* Part II, *J.*, 1949, S 131.

propionitrile (VII; R′ = Me), liberated from its hydrochloride with 4-methylmorpholine, gives 2-amino-3 : 6-dimethylpyrazine 1-oxide (VIII; R = R′ = Me) which was characterised as its picrate. Like the 3 : 5-disubstituted 2-aminopyrazine 1-oxides described by Sharp and Spring (*loc. cit.*) 2-amino-3 : 6-dimethylpyrazine 1-oxide gives an intense blue colour with aqueous ferric chloride which is discharged on the addition of acid. Reduction of 2-amino-3 : 6-dimethylpyrazine 1-oxide with sodium dithionite gives 3-amino-2 : 5-dimethylpyrazine (IX; R = R′ = Me) characterised as its picrate.

$$\underset{\text{(XI.)}}{(EtO)_2CH{\cdot}COR} \longrightarrow \underset{\text{(XII.)}}{(EtO)_2CH{\cdot}\overset{\overset{|}{N}\cdot OH}{\overset{|}{C}}R} \longrightarrow \underset{\text{(VI.)}}{OHC{\cdot}\overset{\overset{|}{N}\cdot OH}{\overset{|}{C}}R}$$

Condensation of α-amino-γ-methylvaleronitrile (DL-leucine nitrile) (VII; R′ = Bu^i) with β-methyl-α-oximino-*n*-valeraldehyde (VI; R = Bu^s) gives 2-amino-3-*iso*butyl-6-*sec.*-butylpyrazine 1-oxide (VIII; R = Bu^s, R′ = Bu^i) characterised as its flavianate. Reduction of this amino-oxide with sodium dithionite gives 3-amino-2-*iso*butyl-5-*sec.*-butylpyrazine (IX; R = Bu^s, R′ = Bu^i) characterised as its picrate. Treatment of the amino-pyrazine with nitrous acid gave 2-*iso*butyl-5-*sec.*-butyl-3-hydroxypyrazine (X; R = Bu^s, R′ = Bu^i) which gives a 6-phenylazo-derivative. 2-*iso*Butyl-5-*sec.*-butyl-3-hydroxypyrazine is undepressed in melting point when mixed with racemic deoxyaspergillic acid and similarly no depression is observed when its 6-phenylazo-derivative is mixed with that of racemic deoxyaspergillic acid. The identity was confirmed by comparison of the ultra-violet absorption spectra of the two specimens.

Experimental.

The method of Johnson and Cretcher (*J. Amer. Chem. Soc.*, 1915, **37**, 2144) for the preparation of ethyl diethoxyacetate proved unsatisfactory. The following method gave reproducible yields: Ethyl dichloroacetate (162 g.) was added dropwise during 30 minutes to a boiling solution of sodium ethoxide from sodium (46 g.) and ethanol (1 l.). The reaction mixture was heated under reflux for 1 hour and set aside overnight. After removal of salt, the solution was evaporated under reduced pressure. The residue was treated with water (250 c.c.) and extracted with ether (4 × 100 c.c.), and the combined extracts were dried (Na_2SO_4). Removal of the ether followed by distillation gave ethyl diethoxyacetate (40—44 g., 22—25%), b. p. 85—95°/13 mm. Ethyl γ-diethoxyacetoacetate, methylglyoxal diethyl acetal, and *sec.*-butylglyoxal diethyl acetal were prepared as described by Dakin and Dudley (*loc. cit.*).

α-*Oximinopropaldehyde Diethyl Acetal.**—(*a*) Methylglyoxal diethyl acetal (2·4 g.) was heated under reflux in ethanol (100 c.c.) containing hydroxylamine [from the hydrochloride (1·16 g.) and sodium ethoxide from sodium (0·38 g.)] for 2 hours. Removal of the solvent and distillation of the residue gave α-*oximinopropaldehyde diethyl acetal* (1·85 g.) as a colourless oil, b. p. 105°/8 mm., n_D^{14} 1·4388 (Found: C, 52·4; H, 9·3; N, 8·7. $C_7H_{15}O_3N$ requires C, 52·2; H, 9·4; N, 8·7%).

(*b*) A solution of hydroxylamine hydrochloride (7·4 g.) in water (30 c.c.) was added during 15 minutes to a mixture of methylglyoxal diethyl acetal (14·0 g.), methanol (20 c.c.), water (90 c.c.), and anhydrous sodium carbonate (7·7 g.), with stirring at 15°. Stirring was continued for 3 hours and the reaction mixture kept overnight. The mixture was extracted with ether (4 × 50 c.c.), and the extract dried (Na_2SO_4) and evaporated. Distillation of the residue gave the oxime acetal (15·5 g.), b. p. 105°/8 mm.

α-*Oximinopropaldehyde.**—α-Oximinopropaldehyde diethyl acetal (1·8 g.) was warmed on the steam-bath for 10 minutes with a buffer solution (10 c.c.; 1·0M-acetic acid and 0·1M-sodium acetate; pH 3·5), a positive test being then given with Fehling's solution. The cooled solution was saturated with salt and extracted with ether (4 × 10 c.c.). The dried (Na_2SO_4) extract was evaporated and the residue distilled, to give a colourless viscous oil (0·8 g.), b. p. 70—75°/20 mm., which rapidly solidified. Crystallisation from light petroleum (b. p. 60—80°) gave α-*oximinopropaldehyde* as prisms, m. p. 67° (Found: C, 41·1; H, 5·8. $C_3H_5O_2N$ requires C, 41·4; H, 5·7%). α-Oximinopropaldehyde sublimes very readily and decomposes on long storage.

β-*Methyl*-α-*oximino*-n-*valeraldehyde Diethyl Acetal.*—A well-stirred mixture of *sec.*-butylglyoxal diethyl acetal (30·0 g.; Dakin and Dudley, *loc. cit.*), methanol (250 c.c.), water (120 c.c.), and anhydrous sodium carbonate (12·75 g.) was treated with a solution of hydroxylamine hydrochloride (12·3 g.) in water (60 c.c.). The mixture (pH ~8) was stirred at room temperature for 26 hours and evaporated under reduced pressure at room temperature. The residue was extracted with ether (4 × 50 c.c.), and the extract dried (Na_2SO_4). Removal of the ether followed by distillation of the residue gave β-*methyl*-α-*oximino*-n-*valeraldehyde diethyl acetal* (29·5 g.) as a colourless oil, b. p. 103°/2 mm., n_D^{15} 1·4459 (Found: C, 59·2; H, 10·0. $C_{10}H_{21}O_3N$ requires C, 59·1; H, 10·4%).

β-*Methyl*-α-*oximino*-n-*valeraldehyde.*—The diethyl acetal (15·0 g.) was heated in methanol (100 c.c.) and buffer solution (100 c.c.; 1·0M-acetic acid and 0·1M-sodium acetate; pH 3·5) under reflux for 4 hours. Methanol was removed under reduced pressure, water (100 c.c.) added, and the mixture extracted with ether (4 × 50 c.c.). The dried ($MgSO_4$) extract was evaporated and the residue distilled to give β-*methyl*-α-*oximino*-n-*valeraldehyde* (6·1 g., 64%) as a pale yellow viscous oil, b. p. 70—74°/1·5 mm., n_D^{15} 1·4737 (Found: C, 55·25; H, 8·2. $C_5H_{11}O_2N$ requires C, 55·8; H, 8·6%).

* Preparations marked * were first made in 1945 in Manchester University by Dr. R. A. Baxter.

2-Amino-3 : 6-dimethylpyrazine 1-Oxide.—A suspension of α-aminopropionitrile hydrochloride (2·55 g., 1 mol.) in dry chloroform (18 c.c.) was shaken with 4-methylmorpholine (2·64 c.c., 1 mol.) and α-oximinopropaldehyde (2·10 g., 1 mol.) rapidly added. The mixture was heated under reflux for 4 hours and the chloroform evaporated. The residue was dissolved in water (25 c.c.), hydrochloric acid (3N.; 25 c.c.) added, and the solution extracted with ether (4 × 20 c.c.), the ethereal extract being discarded. The aqueous solution was basified (litmus) with sodium carbonate and extracted with ether (4 × 20 c.c.); the ethereal extract, of which the residue on evaporation did not give a blue colour in ethanol with aqueous ferric chloride, was rejected. The aqueous phase was evaporated and the dried, powdered residue extracted with hot chloroform (5 × 50 c.c.). The combined chloroform extracts were evaporated, the gum (450 mg.) was dissolved in ethanol (5 c.c.) and treated with saturated ethanolic picric acid (10 c.c.), and the precipitate (290 mg.) collected. Three crystallisations from ethanol gave *2-amino-3 : 6-dimethylpyrazine 1-oxide picrate* as yellow felted needles, m. p. 220° (decomp.) (Found : C, 39·4; H, 3·3; N, 22·5. $C_6H_9ON_3,C_6H_3O_7N_3$ requires C, 39·1; H, 3·3; N, 22·8%). An ethanolic solution of the picrate gave a greenish-blue colour with aqueous ferric chloride discharged by dilute hydrochloric acid. The picrate (290 mg.) was dissolved in warm hydrochloric acid (3N.; 20 c.c.), and the solution extracted with ethyl acetate (4 × 10 c.c.) to remove picric acid. The aqueous solution was evaporated to dryness, the residue (151 mg.) dissolved in water (1 c.c.), and the solution basified (litmus) with sodium carbonate solution and evaporated to dryness. Sublimation of the residue at 110—120°/10^{-4} mm. gave a crystalline sublimate (85 mg.), m. p. 160—162°. Two further sublimations gave *2-amino-3 : 6-dimethylpyrazine 1-oxide* as needles, m. p. 165° (Found : C, 51·7; H, 6·2; N, 29·5. $C_6H_9ON_3$ requires C, 51·8; H, 6·5; N, 30·2%). Light absorption in ethanol : Maxima at 2320 (ε = 23,600) and 3290 A. (ε = 7800). The oxide is readily soluble in water and ethanol and sparingly soluble in ether, light petroleum (b. p. 60—80°), and benzene; its aqueous or ethanolic solution gives an intense blue colour with aqueous ferric chloride, the colour being discharged by addition of dilute hydrochloric acid.

3-Amino-2 : 5-dimethylpyrazine.—A solution of 2-amino-3 : 6-dimethylpyrazine 1-oxide (35 mg.) in water (2 c.c.) was heated under reflux with sodium dithionite (0·32 g.). After 1 hour the cooled solution was again treated with dithionite (0·32 g.) and the refluxing continued. Six similar additions were made and water was added (2 × 0·5 c.c.) at intervals to maintain complete solution. The reaction mixture was diluted with water to a bulk of 10 c.c., made alkaline (litmus) with 2N-sodium hydroxide, and extracted with ether (6 × 10 c.c.). The dried (Na_2SO_4) ethereal solution was evaporated, the residue dissolved in ethanol (1 c.c.), and the filtered solution treated with saturated ethanolic picric acid (0·5 c.c.) whereupon 3-amino-2 : 5-dimethylpyrazine picrate (10 mg.) separated as yellow prismatic needles, m. p. 205—206° alone or mixed with a specimen prepared as described by Newbold, Spring, and Sweeny (*J.*, 1949, 302).

DL-*Leucine Nitrile Hydrochloride.*—A solution of *iso*valeraldehyde (25 g.) in ether (145 c.c.) was stirred with ammonium chloride (17·4 g.) at 0° and a solution of potassium cyanide (19·4 g.) in water (50 c.c.) was added during 15 minutes. After 4 hours' stirring at 0° the ether was separated and the aqueous phase extracted with ether (3 × 50 c.c.). The combined ethereal solution was dried (Na_2SO_4) at 0° and saturated with dry hydrogen chloride at 0°. The precipitate (11·4 g.) was collected, dried *in vacuo* over sodium hydroxide, and used for the next stage without further purification. A specimen was thrice crystallised from acetone from which DL-*leucine nitrile hydrochloride* separated as plates, m. p. 175—180° with darkening (Found : C 48·9; H, 8·7. $C_6H_{13}N_2Cl$ requires C, 48·5; H, 8·8%).

2-Amino-3-isobutyl-6-sec.-butylpyrazine 1-Oxide.—DL-Leucine nitrile hydrochloride (6·65 g.), suspended in dry chloroform (25 c.c.), was shaken with 4-methylmorpholine (4·95 c.c.), and the mixture treated with a solution of β-methyl-α-oximino-*n*-valeraldehyde (5·8 g.) in dry chloroform (7·5 c.c.). The mixture was heated under reflux for 4 hours, cooled, and filtered and the filtrate evaporated. The residue was dissolved in ether (75 c.c.) and extracted with hydrochloric acid (4 × 25 c.c.; 3N.). The hydrochloric acid solution was extracted with ether (2 × 30 c.c.) (the ethereal extract being rejected), basified (litmus) with sodium hydroxide solution, and extracted with ether (4 × 50 c.c.). The ethereal solution was washed with water (3 × 15 c.c.), dried (Na_2SO_4), and evaporated to give a viscous oil (3·12 g.), distillation of which gave *2-amino-3-isobutyl-6-sec.-butylpyrazine 1-oxide* as a light yellow oil, b. p. 150—155°/0·5 mm., n_D^{15} 1·5410 (Found : C, 64·8; H, 9·9. $C_{12}H_{21}ON_3$ requires C, 64·6; H, 9·4%). It is very soluble in the common organic solvents, insoluble in water, and soluble in 3N-hydrochloric acid; its ethanolic solution gives a deep blue colour with aqueous ferric chloride, discharged by dilute hydrochloric acid. The *flavianate* crystallises from 50% aqueous ethanol as light yellow prisms, m. p. 235° (decomp.) (Found : C, 49·5; H, 5·2; N, 12·4. $C_{12}H_{21}ON_3,C_{18}H_4O_8N_2S$ requires C, 49·2; H, 5·1; N, 13·0%).

3-Amino-2-isobutyl-5-sec.-butylpyrazine.—A solution of 2-amino-3-*iso*butyl-6-*sec.*-butylpyrazine 1-oxide (1·4 g.) in ethanol (15 c.c.) and water (15 c.c.) was treated with sodium dithionite (2 g.) and heated under reflux for 30 hours during which time 20 additions of sodium dithionite (1 g.), ethanol (5 c.c.), and water (5 c.c.) were made at approximately equal intervals. Ethanol was removed under reduced pressure, and the residue made alkaline with 3N-sodium hydroxide and extracted with ether (4 × 30 c.c.). The combined extracts were washed with water (25 c.c.) and dried ($MgSO_4$). Removal of the ether gave an amber-coloured oil, which gave a faint blue colour with aqueous-alcoholic ferric chloride. A solution of the oil in ethanol (5 c.c.) was treated with saturated ethanolic picric acid, and the precipitate (1·15 g.) collected. Crystallisation from ethanol gave *3-amino-2-isobutyl-5-sec.-butylpyrazine picrate* as yellow felted needles, m. p. 120—121° (Found : C, 49·9; H, 5·2; N, 19·6. $C_{12}H_{21}N_3,C_6H_3O_7N_3$ requires C, 49·5; H, 5·5; N, 19·3%).

2-isoButyl-5-sec.-butyl-3-hydroxypyrazine.—A solution of 3-amino-2-*iso*butyl-5-*sec.*-butylpyrazine picrate (400 mg.) in hot ethanol (5 c.c.) was treated with hydrochloric acid (10 c.c.; 3N.), and the ethanol removed by evaporation. The mixture was diluted with water (10 c.c.) and extracted with ethyl acetate

(2 × 10 c.c.). The aqueous phase was evaporated to dryness under reduced pressure, the solid residue dissolved in hydrochloric acid (5 c.c.; 3N.), and the solution cooled to 0° and treated with sodium nitrite (0·25 g.) added in portions over 5 minutes. The reaction mixture was kept at 0° for 30 minutes, heated to 50—60° for 5 minutes, neutralised (litmus) with solid sodium carbonate, and extracted with ether (2 × 10 c.c.). The ethereal extract was washed with potassium hydroxide solution (2 × 5 c.c.; 2N.), and the combined aqueous layers were neutralised (litmus) with hydrochloric acid (3N.). The precipitated solid (65 mg.; m. p. 96—98°) was crystallised from aqueous ethanol, to give 2-*iso*butyl-5-*sec.*-butyl-3-hydroxypyrazine as prismatic needles, m. p. 100·5—101·5°. A mixture with racemic deoxyaspergillic acid, m. p. 103—104° (Dunn *et al.*, *loc. cit.*) had m. p. 101·5—102° (Found: C, 69·5; H, 9·6; N, 13·4. Calc. for $C_{12}H_{20}ON_2$: C, 69·2; H, 9·6; N, 13·5%). Light absorption in ethanol: Maxima at 2270 (ε = 8000) and 3240 A (ε = 8000). The 6-phenylazo-derivative separated from aqueous ethanol as red needles, m. p. 188—189° alone or mixed with the 6-phenylazo-derivative of racemic deoxyaspergillic acid, m. p. 188—190° (Found: C, 69·65; H, 7·5. Calc. for $C_{18}H_{24}ON_4$: C, 69·3; H, 7·7%).

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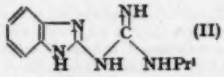
596. *The Reaction of "Paludrine" (Proguanil) with Ethyl Acetoacetate.*

By GEORGE P. FRASER and WILLIAM O. KERMACK.

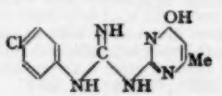
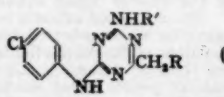
Proguanil ("Paludrine") (I; R = Pr^i) and ethyl acetoacetate yield 3-*p*-chlorophenyl-3:4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine (V) and 6-acetonyl-2-*p*-chloroanilino-4-*iso*propylamino-*s*-triazine (IV; R = Ac, R′ = Pr^i). The former product has also been synthesised by a route which establishes its structure. Alkaline hydrolysis of the triazine yields 2-*p*-chloroanilino-6-methyl-4-*iso*propylamino-*s*-triazine (IV; R = H, R′ = Pr^i) which is also obtained from proguanil and acetic anhydride.

EVIDENCE has been adduced by Hawking and Perry (*Brit. J. Pharmacol.*, 1948, **3**, 320) that "Paludrine" (proguanil B.P.C.) (I; R = Pr^i) does not act directly on the malarial parasite, but that it is first converted, probably in the liver of the host, into an active derivative. When the present work was begun it was known that various possible metabolic products of proguanil such as the benziminazole (II) (King, Acheson, and Spensley, *J.*, 1948, 1366) were without antimalarial activity and there was no definite indication as to what the active product might be. The possibility fell to be considered that proguanil was activated, not by undergoing

(I) (II) 

some process of oxidation or dehydrogenation, but by condensation of the diguanyl side chain with some normal metabolite. Such a metabolite which might readily condense with proguanil, was acetoacetic acid which is an intermediate product of fatty acid metabolism. It was therefore considered desirable to examine the reaction between proguanil and ethyl acetoacetate to ascertain whether any of the products possessed antimalarial activity.

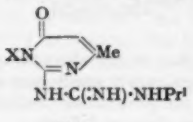
The general idea that some such condensation might be involved in the activation of proguanil was supported by the well-known fact that N^1-*p*-chlorophenyldiguanide (I; R = H) is devoid of antimalarial activity whereas the 5-alkyl derivatives are active. It appeared possible that, in the absence of the 5-alkyl group, condensation with the β-keto-acid might occur in such a way as to involve the 5-nitrogen atom, whereas when this position was substituted by an alkyl group, condensation not involving N^5 might be favoured. Curd and Rose (*J.*, 1946, 362) had already shown that the main product of the reaction between N^1-*p*-

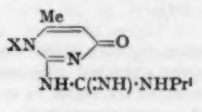
(III)  (IV) 

chlorophenyldiguanide and ethyl acetoacetate was the pyrimidine (III) involving the atoms N^4 and N^5 in the condensation, accompanied by a small quantity of the triazine (IV; R = Ac, R′ = H) involving N^3 and N^4 or N^5. When proguanil and ethyl acetoacetate were heated

together in equimolecular proportions a crystalline solid was obtained in 10—15% yield. When an excess of ethyl acetoacetate was employed the yield of this compound could be increased to about 30% calculated on proguanil. The rest of the product was a brown viscous oil. The crystalline product, m. p. 299—300° (decomp.), had the formula $C_{16}H_{16}ON_5Cl$ and was evidently formed from one molecule of each of the reactants by the loss of one molecule of water and one of ethanol.

Hydrolysis of this compound with 2·5N-hydrochloric acid yielded a crystalline product $C_{11}H_9O_2N_3Cl$, m. p. *ca.* 342° (decomp.). As this contained two nitrogen atoms it appeared most probably to be a pyrimidine derivative. During the treatment with hydrochloric acid three nitrogen atoms had been lost but the *p*-chlorophenyl group had been retained. Presumably the compound, m. p. 299—300°, contained the pyrimidine nucleus and of the two nitrogen atoms in that nucleus, one must be N^1 as otherwise the *p*-chlorophenyl group could not have been retained on hydrolysis. Thus, of the five nitrogen atoms of proguanil, those involved in the condensation with ethyl acetoacetate must be N^1 and either N^3 or N^5. The formulæ (V, VI, VII, and VIII) are therefore possible for the compound, m. p. 299—300°. Hydrolysis of (V) or (VII) would yield (IX), whilst (VI) or (VIII) would yield (X). It was therefore decided to synthesise (IX) and (X) by unambiguous methods so as to determine the structure of the hydrolytic product.


(V)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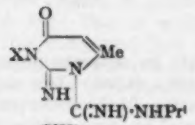
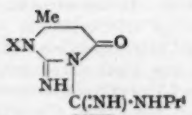
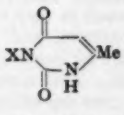
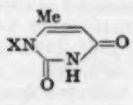
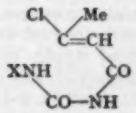

(VII)


(VIII)


(IX)

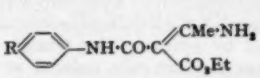

(X)

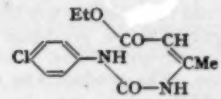

(XI)

(X = *p*-C_6H_4Cl)

1-*p*-Chlorophenyl-6-methyluracil (X) was synthesised by heating β-chlorocrotonyl chloride (Shriner and Keyser, *J. Amer. Chem. Soc.*, 1938, **60**, 286) with *p*-chlorophenylurea to give *N*-β-chlorocrotonyl-*N'*-*p*-chlorophenylurea (XI). This cyclized in refluxing pyridine to give 1-*p*-chlorophenyl-6-methyluracil, m. p. 143°, which was not identical with the hydrolytic product.

The isomer (IX) was synthesised as follows. Behrend, Meyer, and Buchholz (*Annalen*, 1901, **314**, 209) synthesised 6-methyl-3-phenyluracil from phenyl *iso*cyanate and ethyl β-aminocrotonate, the compound (XII; R = H) being obtained as a by-product. When equimolecular

(XII) 

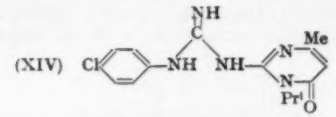

(XIII)

proportions of *p*-chlorophenyl *iso*cyanate and ethyl β-aminocrotonate were heated together in the presence of a trace of triethylamine, ethyl β-*N'*-*p*-chlorophenylureidocrotonate (XIII) was formed, which on further heating cyclized to 3-*p*-chlorophenyl-6-methyluracil (IX), m. p. *ca.* 342° (decomp.). This gave no depression of the melting point of the hydrolytic product obtained above. It seemed likely therefore that the hydrolytic product was 3-*p*-chlorophenyl-6-methyluracil but in view of its high melting point and rather wide decomposition range further evidence was required. This was kindly furnished by Dr. H. C. Carrington, Imperial Chemical Industries Limited, Dyestuffs Division, Blackley, Manchester, who had examined them and reported the ultra-violet spectra of the substances to be identical.

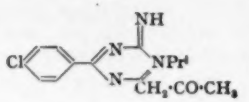
It follows that the condensation product, m. p. 299—300°, must be either (V) or (VII). Of these structures, (V) was considered the more probable both because in proguanil N^3 might be expected to be more reactive than N^5 and also because the formation of (IX) from (V)

appeared to be more probable than that from (VII). One puzzling observation may be mentioned here, however, which emphasised the need for considering both possibilities. The maximum yield of the uracil derivative, m. p. 342°, from the hydrolysis of the condensation product, m. p. 299—300°, never exceeded 30%. It was observed that the filtrate from the hydrolysis after removal of the uracil contained a diazotisable amino-group and finally *p*-chloroaniline was isolated. Colorimetric observations showed that this amine might account for 35% of the original compound. It appeared surprising that fission of the pyrimidine ring should take place with such relative ease. Prolonged boiling of 3-*p*-chlorophenyl-6-methyluracil (IX) with 2·5N-hydrochloric acid showed that, with this pyrimidine derivative, ring fission with liberation of *p*-chloroaniline took place only slowly, 3·3% being liberated in 8 hours. This result excluded the possibility that ring fission occurred after removal of the side chain.

A possibility which had to be considered was that the condensation product, m. p. 299—300°, was a mixture of two isomers, one of which was (V) or (VII) and the other a pyrimidine or triazine derivative carrying a *p*-chloroanilino-group as a side chain, as in (XIV). Numerous



(XIV)



(XV)

attempts to separate possible isomers by fractional crystallisation or by chromatography completely failed. The only impurity detected was an occasional very small quantity of proguanil. In the circumstances it seemed advisable to synthesise the pyrimidine condensation compound by some independent and unambiguous route. This was done as follows.

Behrend, Meyer, and Buchholz (*loc. cit.*) reported that phenyl *iso*thiocyanate and ethyl β-aminocrotonate gave 6-methyl-3-phenyl-2-thiouracil in very small yield. In our experiments *p*-chlorophenyl *iso*thiocyanate, ethyl β-aminocrotonate, and a trace of triethylamine were heated rapidly to 150° and kept at this temperature for one hour. 3-*p*-Chlorophenyl-6-methyl-2-thiouracil was obtained although in poor yield. This compound was methylated readily with methyl iodide and sodium ethoxide, to give 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-methylthiopyrimidine, which when heated with *iso*propylguanidine (Crowther, Richardson, and Rose, *J.*, 1948, 1641) lost methanethiol to give 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine (V), m. p. 299—300°, giving no depression of the melting point with the original condensation compound.

Confirmation of the structure of the 2-methylthiopyrimidine was obtained when the reaction with *iso*propylguanidine was carried out in aqueous ethanol. A very low yield of the 2-*iso*propylguanidino-compound was obtained and it was found that hydrolysis of the 2-methylthiopyrimidine had taken place, methanethiol having been lost and 3-*p*-chlorophenyl-6-methyluracil, identical with that synthesised above, obtained.

It must be concluded therefore that the condensation compound is undoubtedly (V) and that the guanidino-group facilitates the fission of the ring with the formation of *p*-chloroaniline.

Advantage was taken of the availability of 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-methylthiopyrimidine to synthesise 3-*p*-chlorophenyl-2-2′-diethylaminoethylamino-3 : 4-dihydro-4-keto-6-methylpyrimidine. This was effected by refluxing the former with diethylaminoethylamine. The product was an oil and was conveniently isolated as its dihydrobromide, m. p. 253°.

The brown viscous oil obtained in the condensation of proguanil and ethyl acetoacetate yielded an amorphous hydrochloride from which alkali liberated a weak base, $C_{15}H_{18}ON_5Cl$, m. p. 121°, in which all five nitrogen atoms of proguanil were retained. When boiled with alkali this yielded a product, $C_{13}H_{14}N_5Cl$, m. p. 173·5—174°, an acetyl group having been lost and the five nitrogen atoms and the *p*-chlorophenyl and *iso*propyl groups retained. These facts strongly suggested these substances to be triazines.

6-Acetonyl-4-amino-2-*p*-chloroanilino-*s*-triazine (IV; R = Ac, R′ = H), obtained by Curd and Rose (*loc. cit.*) in the reaction of *p*-chlorophenyldiguanide and ethyl acetoacetate, was converted by boiling dilute alkali into 4-amino-2-*p*-chloroanilino-6-methyl-*s*-triazine (IV; R = R′ = H). This triazine was also obtained by treatment of *p*-chlorophenyldiguanide with acetic anhydride. We have found that when proguanil was treated with acetic anhydride 2-*p*-chloroanilino-6-methyl-4-*iso*propylamino-*s*-triazine (IV; R = H, R′ = Pr^i) was formed

which gave no depression of melting point with the product, m. p. 173·5—174°, obtained as above by alkaline hydrolysis. This indicated the original compound to be 6-acetonyl-2-*p*-chloroanilino-4-*iso*propylamino-*s*-triazine (IV; R = Ac, R′ = Pr^i). The other possible formulation, where N^3 and N^5 of proguanil are involved in the ring so as to give the imino-derivative (XV), appeared less likely but required consideration. Prolonged acid and alkaline hydrolysis of the substance produced, however, little decomposition and no new compound could be isolated. Cuthbertson and Moffatt (*J.*, 1948, 561) obtained 6-chloro-2-*p*-chloroanilino-4-*iso*propylamino-*s*-triazine by successive replacement of the two chlorine atoms in cyanuric chloride by *p*-chloroaniline and *iso*propylamine, respectively. The chlorine atom in the 6-position could not be replaced by hydrogen, except by methods of reduction which also removed the chlorine atom of the benzene ring to give 2-anilino-4-*iso*propylamino-*s*-triazine. By heating proguanil with ethyl formate they obtained a triazine which on dechlorination yielded 2-anilino-4-*iso*propylamino-*s*-triazine. Here clearly the ethyl formate has reacted with N^3 and N^4 of the diguanide system. It appears safe to conclude from this analogy that ethyl acetoacetate similarly reacts with N^3 and N^4 and that the resulting compound has the structure (IV; R = Ac, R′ = Pr^i).

Antimalarial tests of 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine have been kindly carried out in the Biological Laboratories of Imperial Chemical Industries Limited. The compound shows slight antimalarial activity against *P. gallinaceum* infections in chicks. The activity, however, is substantially less than that of proguanil, apparently excluding the possibility that this might be the active compound into which proguanil is converted in the animal body. 6-Acetonyl-2-*p*-chloroanilino-4-*iso*propylamino- and 2-*p*-chloroanilino-6-methyl-4-*iso*propylamino-*s*-triazine have been found to be inactive.

Experimental.

Condensation of Proguanil and Ethyl Acetoacetate.—Proguanil (31·2 g.) and ethyl acetoacetate (150 c.c.) were refluxed for 5 hours. Most of the excess of ethyl acetoacetate was removed by distillation under reduced pressure, leaving a thick yellow paste. This was filtered and the residue washed with ether (2 × 100 c.c.). The filtrate and washings were combined and left overnight and a further precipitate filtered off, washed, and combined with the first. This material was recrystallised from a large volume of ethanol, from which 3-p-*chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-*isopropylguanidinopyrimidine* (V) separated as a microcrystalline powder, m. p. 299—300° (decomp.) (12·2 g., 30·1%) (Found: C, 56·4; H, 5·9; N, 22·4; Cl, 10·9. $C_{15}H_{14}ON_5Cl$ requires C, 56·3; H, 5·7; N, 21·9; Cl, 11·2%).

The mother-liquor yielded, after removal of the ether, a brown viscous oil which slowly hardened to a glass. This was dissolved in acetone (200 c.c.), and concentrated hydrochloric acid (20 c.c.) was added. The hydrochloride which separated overnight was filtered off and recrystallised from water acidified with a few drops of hydrochloric acid. The white amorphous hydrochloride (14·2 g.) melted at 242—245°. This was stirred with acetone (30 c.c.), and sufficient 2·5N-sodium hydroxide added to liberate the base, which dissolved in the acetone to give a clear solution. The base was precipitated by the addition of much water, filtered off, washed with water, and recrystallised from light petroleum (b. p. 40—60°), from which 6-*acetonyl*-2-p-*chloroanilino*-4-*isopropylamino*-*s*-*triazine* (IV; R = Ac, R′ = Pr^i) separated as fine white crystals (10·2 g.), m. p. 121° (Found: C, 56·8; H 5·4; N, 21·6; Cl, 11·3. $C_{15}H_{18}ON_5Cl$ requires C, 56·3; H, 5·7; N, 21·9; Cl, 11·2%).

Hydrolysis of 3-p-*Chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-*isopropylguanidinopyrimidine* (V).—3-*p*-Chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanylpyrimidine (2·0 g.) was boiled with 2·5N-hydrochloric acid (20 c.c.) for 0·5 hour. 3-p-*Chlorophenyl*-6-*methyluracil*, which was precipitated during the hydrolysis, was filtered off and crystallised from ethanol–water as shining plates, m. p. 342° (decomp.) (0·43 g.) (Found: C, 55·6; H, 3·9; N, 12·4; Cl, 15·65. $C_{11}H_9O_2N_2Cl$ requires C, 55·8; H, 3·8; N, 11·95; Cl, 15·0%).

Hydrolysis of 6-*Acetonyl*-2-p-*chloroanilino*-4-iso*propylamino*-*s*-*triazine* (IV; R = Ac, R′ = Pr^i).—6-Acetonyl-2-*p*-chloroanilino-4-*iso*propylamino-*s*-triazine (5 g.) was refluxed with 2·5N-sodium hydroxide (20 c.c.) and ethanol (20 c.c.) for 1 hour. The alcohol was boiled off. The precipitate of 2-p-*chloroanilino*-6-*methyl*-4-iso*propylamino*-*s*-*triazine* recrystallised from light petroleum (b. p. 100—120°) as white hemispherical rosettes (on the walls of the flask), m. p. 173·5—174° (Found: C, 56·4; H, 5·8; N, 24·8; Cl, 13·0. $C_{12}H_{14}N_5Cl$ requires C, 56·2; H, 5·8; N, 25·2; Cl, 12·8%).

2-p-*Chloroanilino*-6-*methyl*-4-iso*propylamino*-*s*-*triazine* (IV; R = H, R′ = Pr^i).—Proguanil (2·0 g.) and acetic anhydride (5·0 c.c.) were heated at 100° for 1 hour. The solution was cooled, diluted with water (30 c.c.), and made alkaline with 2·5N-sodium hydroxide. The precipitate was filtered off, washed with water, and boiled with 10N-sodium hydroxide (2 c.c.) in methanol (30 c.c.) for 3 minutes. The solution was cooled and water (30 c.c.) added. The precipitate of 2-*p*-chloroanilino-6-methyl-4-*iso*propylamino-*s*-triazine was recrystallised from light petroleum (b. p. 100—120°); it had m. p. 173·5—174° (yield, 1·04 g.) (Found: C, 55·9; H, 6·2; N, 25·3; Cl, 12·5%). This triazine gave no depression of the m. p. with the triazine derived as above.

N-*β*-*Chlorocrotonyl*-N′-p-*chlorophenylurea* (XI).—*β*-Chlorocrotonyl chloride (13·9 g.), *p*-chlorophenylurea (17·5 g.), and benzene (50 c.c.) were refluxed in a water-bath for 10 hours. The benzene

was boiled off and the product recrystallised from chlorobenzene. **N-β-*Chlorocrotonyl*-N'-p-*chlorophenylurea*** was obtained as needles, m. p. 243·5—244·5° (13·6 g.) (Found: C, 48·9; H, 4·1; N, 10·3; Cl, 25·3. $C_{11}H_{10}O_2N_2Cl_2$ requires C, 48·4; H, 3·7; N, 10·3; Cl, 26·0%).

1-p-*Chlorophenyl*-6-*methyluracil* (X).—*N*-Chlorocrotonyl-*N'*-*p*-chlorophenylurea (8·2 g.) was heated under reflux in pyridine (20 c.c.) for 1·5 hours. Most of the pyridine was removed under reduced pressure, leaving a thick dark red syrup. This was dissolved in alcohol (10 c.c.) and treated with charcoal. After several recrystallisations from alcohol, **1-p-*chlorophenyl*-6-*methyluracil*** separated as long feathery needles, m. p. 143° (4·2 g.) (Found: C, 56·1; H, 3·9; N, 11·6; Cl, 15·0. $C_{11}H_9O_2N_2Cl$ requires C, 55·8; H, 3·8; N, 11·95; Cl, 15·0%).

Ethyl* β-(N'-p-*Chlorophenylureido*)*crotonate (XIII).—*p*-Chlorophenyl *iso*cyanate (9·2 g.) and ethyl β-aminocrotonate (7·8 g.) were melted together in a water-bath at 50°, in the presence of a trace of triethylamine as catalyst. The mixture was left at room temperature for 20 minutes after which the solid product was fractionally crystallised from alcohol, from which ***ethyl* β-(N'-p-*chlorophenylureido*)-*crotonate*** separated as colourless prisms, m. p. 135° (5·6 g.) (Found: C, 55·4; H, 5·5; N, 10·2; Cl, 12·6. $C_{13}H_{15}O_3N_2Cl$ requires C, 55·3; H, 5·3; N, 9·9; Cl, 12·4%). Evaporation of the mother-liquors and recrystallisation of the solid product from light petroleum (b. p. 80—100°) yielded ***ethyl* β-*amino*-α-p-*chlorophenylcarbamylcrotonate*** (XII; R = Cl), crystallising in tufted needles, m. p. 161° (Found: C, 55·75; H, 5·4; N, 10·2. $C_{13}H_{15}O_3N_2Cl$ requires C, 55·3; H, 5·3; N, 9·9%).

3-p-*Chlorophenyl*-6-*methyluracil* (IX).—Ethyl β-(*N'*-*p*-chlorophenylureido)crotonate (5·6 g.), when heated in an oil-bath at 150° for 3 hours in the presence of a trace of pyridine or triethylamine gave **3-*p*-chlorophenyl-6-methyluracil** (3·5 g., 23·8%), m. p. 342° (decomp.), as shining plates (Found: C, 55·85; H, 4·0; N, 12·1. $C_{11}H_9O_2N_2Cl$ requires C, 55·8; H, 3·8; N, 11·95%). Its m. p. was not depressed by the addition of the hydrolysis product from **3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine**, but charring took place around the m. p.

3-p-*Chlorophenyl*-6-*methyl*-2-*thiouracil*.—*p*-Chlorophenyl *iso*thiocyanate (16·9 g.), ethyl β-aminocrotonate (12·9 g.), and a few drops of triethylamine were heated rapidly to 150°. After 1 hour the resulting dark brown oil was cooled and the precipitate of **3-*p*-chlorophenyl-6-methyl-2-thiouracil** filtered off. Ether (50 c.c.) was added to the filtrate and it was left overnight in the refrigerator. The resulting precipitate was filtered off, washed with ether (10 c.c.) and combined with the first yield. This product, recrystallised from alcohol–water, gave **3-p-*chlorophenyl*-6-*methyl*-2-*thiouracil*** (7·4 g.) as a fine pale yellow powder, m. p. 275—280° (decomp.) (Found: C, 52·3; H, 3·6; N, 11·3; Cl, 14·2. $C_{11}H_9ON_2SCl$ requires C, 52·3; H, 3·6; N, 11·1; Cl, 14·0%).

3-p-*Chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-*methylthiopyrimidine*.—To a solution of sodium ethoxide [from sodium (0·38 g.) in alcohol (30 c.c.)] was added **3-*p*-chlorophenyl-6-methyl-2-thiouracil** (4·2 g.) and methyl iodide (3·2 g., 1·25 mols.). The mixture was refluxed for 1 hour during which the methyl derivative started to crystallise. Cooling and filtering the solution, and recrystallising the product from alcohol–water gave **3-p-*chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-*methylthiopyrimidine*** (4·3 g., 97·7%) as needles, m. p. 151° (Found: C, 53·9; H, 4·3; N, 10·8; Cl, 13·05. $C_{12}H_{11}ON_2ClS$, requires C, 54·0; H, 4·2; N, 10·5; Cl, 13·3%).

3-*p*-*Chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-*isopropylguanidinopyrimidine* (V).—**3-*p*-Chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-methylthiopyrimidine** (2·7 g.) and *iso*propylguanidine (1·0 g.) were heated at 120° for 5 hours. The reaction-tube was evacuated during the final hour of heating to remove the last traces of methanethiol. The resulting white solid was broken up and crystallised from a large volume of alcohol from which **3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine** (2·27 g., 71%) separated as fine needles, m. p. 299—300° (decomp.) (Found: C, 56·3; H, 5·8; N, 22·0; Cl, 10·8. $C_{15}H_{18}ON_5Cl$ requires C, 56·3; H, 5·7; N, 21·9; Cl, 11·2%). This substance did not depress the m. p. of the pyrimidine obtained from the reaction of proguanil and ethyl acetoacetate.

3-p-*Chlorophenyl*-2-2'-*diethylaminoethylamino*-3 : 4-*dihydro*-4-*keto*-6-*methylpyrimidine*.—**3-*p*-Chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-methylthiopyrimidine** (1·08 g.) and 2-diethylaminoethylamine (5 c.c.) were refluxed for 7 hours. Most of the excess of diethylaminoethylamine was removed under reduced pressure, leaving a dark brown oil. This was extracted with 2% acetic acid (100 c.c.) which was then neutralised with aqueous ammonia and extracted with ether (3 × 50 c.c.). The ether was evaporated off at room temperature and the product extracted again in the same way. The resulting pale yellow oil was dried and dissolved in ether (10 c.c.), and anhydrous alcoholic hydrobromic acid added until the solution was just acid. Acetone (75 c.c.) was added and the precipitate of **3-p-*chlorophenyl*-2-2'-*diethylaminoethylamino*-3 : 4-*dihydro*-4-*keto*-6-*methylpyrimidine dihydrobromide***, m. p. 253°, was filtered off (0·54 g.) (Found: C, 41·15; H, 5·2; N, 11·4. $C_{17}H_{23}ON_4ClBr_2$ requires C, 41·1; H, 5·1; N, 11·3%).

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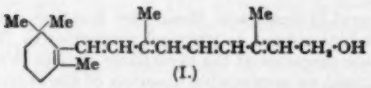
597. *Studies in the Polyene Series. Part XXXVIII.* The Synthesis of Phenyl Analogues of Vitamin A Acid and Vitamin A.*

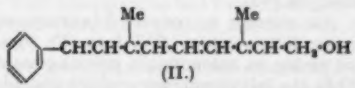
By B. C. L. Weedon and R. J. Woods.

Methods have been devised for the synthesis of crystalline phenyl analogues of vitamin A acid and vitamin A. The acid was isolated in two geometrically isomeric forms, neither of which exhibited growth-promoting properties.

During the last few years the development of new synthetic methods in the polyene field has led to the preparation of a number of structural variants of the vitamin A_1 molecule (I). Growth-promotion tests on such compounds, and on derivatives of the vitamin itself, have furnished considerable information concerning the effect on biological activity of varying either the structure of the side chain or the nature of the functional group (for a review see Isler, *Chimia*, 1950, **4**, 103). Until recently conclusions regarding the specificity of the 2 : 6 : 6-trimethyl*cyclo*hex-1-enyl ring system have been drawn mainly from biological assays on cyclic and acyclic carotenoids and their degradation products (cf. Jones, *Ann. Reports*, 1940, **37**, 290). The number of structural modifications which can be examined in this way is, however, strictly limited, and furthermore the conclusions are open to criticism since structural features may determine the mode of fission of a carotenoid. The failure of the latter to exhibit activity of the pro-vitamin A type does not necessarily indicate inherent inactivity in the corresponding vitamin A_1 analogue itself (Heilbron, Jones, and Richardson, *J.*, 1949, 287).



(I.)



(II.)

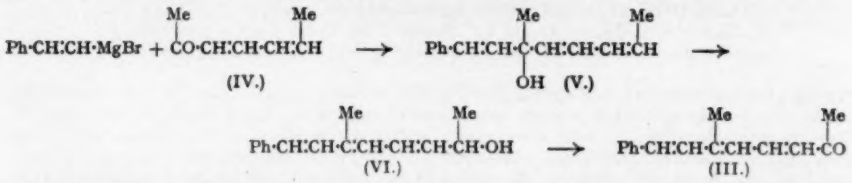
Vitamin A_2 has been shown by growth-promotion tests to possess *ca.* 40% of the biological activity of vitamin A_1 (Shantz and Brinkman, *J. Biol. Chem.*, 1950, **183**, 467). Recently a preliminary account has been published (Farrar, Hamlet, Henbest, and Jones, *Chem. and Ind.*, 1951, 49) of the synthesis of vitamin A_2, confirming its structure as 3′-dehydro-vitamin A_1, possessing an additional double bond in the ring system. A number of acetylenic analogues of vitamin A_1 and the corresponding acid, derived from ethynyl*cyclo*hexenes, have also been observed to exhibit slight, though definite, growth-promoting properties (Heilbron, Jones, and Richardson, *loc. cit.*; Heilbron, Jones, Lewis, Richardson, and Weedon, *J.*, 1949, 742; Heilbron, Jones, Lewis, and Weedon, *J.*, 1949, 2023; Cheeseman, Heilbron, Jones, and Weedon, *J.*, 1949, 3120). The presence in the molecule of an unmodified 2 : 6 : 6-trimethyl*cyclo*hex-1-enyl ring system is therefore not as essential for activity of the vitamin A type as has previously been suggested (cf. Karrer and Jucker, "Carotinoide," Basle, 1948), and the synthesis of compounds differing from vitamin A_1 solely in the nature of the ring system is clearly desirable. Progress in this direction has been reported in previous papers in this series.

Apart from the synthesis of vitamin A_2, the only claim to have prepared a compound containing the vitamin A side chain and a variant of the ring system is that of Linnell and Shen (*J. Pharm. Pharmacol.*, 1949, **1**, 971). These authors substituted benzylideneacetone for β-ionone in the synthesis of vitamin A_1 developed by Isler, Huber, Ronco, and Kofler (*Helv. Chim. Acta*, 1947, **30**, 1911) and obtained a biologically inactive, highly unstable product. This was presumed on the basis of light-absorption measurements to contain the phenyl analogue (II), although purification could not be effected. The present communication records the preparation of crystalline phenyl analogues of vitamin A acid and vitamin A. Comparison of the light-absorption properties of the pure carbinol (II) with those of Linnell and Shen's product indicates that the purity of the latter cannot have exceeded 15%.

An obvious intermediate for the preparation of (II) is the phenyl ketone (III), the corresponding 2 : 6 : 6-trimethyl*cyclo*hexenyl C_{18}-ketone having been used successfully for the synthesis of vitamin A_1 (Arens and van Dorp, *Rec. Trav. chim.*, 1949, **68**, 604; Schwarzkopf, Cahnmann, Lewis, Swidinsky, and Wüest, *Helv. Chim. Acta*, 1949, **32**, 443), and two routes to (III) have now been developed. Preparation of (III) from benzylideneacetone by a route analogous to that employed in the synthesis of the C_{18} ketone was found to be unsatisfactory (Linnell and Shen, *loc. cit.*).

* Part XXXVII, *J.*, 1951, 1074.

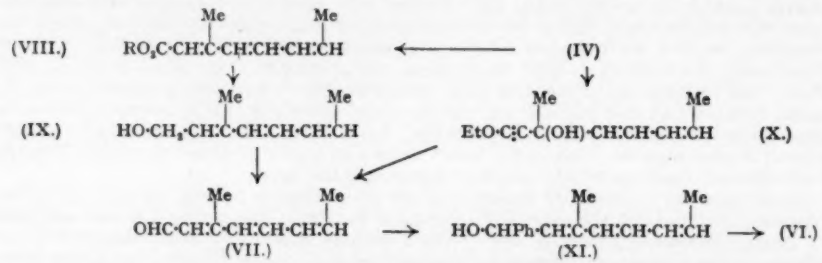
Reaction of styrylmagnesium bromide with the readily available crotonylideneacetone (IV) gave the tertiary alcohol (V), which on treatment with 0·01M-hydrochloric acid underwent anionotropic rearrangement to the crystalline alcohol (VI) (25% overall yield from IV). This was oxidised to the required ketone (III), in 77% yield, by shaking its solution in light petroleum with manganese dioxide according to the elegant method of Ball, Goodwin, and



Morton (*Biochem. J.*, 1948, **42**, 516) for the conversion of vitamin A_1 into retinene. Although few examples of its use have been recorded, this oxidation procedure obviously constitutes a valuable method for the synthesis of both polyene aldehydes (see below; Wendler, Slates, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719; Farrar, Hamlet, Henbest, and Jones, *loc. cit.*) and ketones (Bharucha and Weedon, forthcoming publication; Braude and Forbes, *J.*, in the press).

The structure of (VI) was confirmed by quantitative hydrogenation, which indicated the presence of three double bonds, and by the alternative synthesis, described below, from the C_9 aldehyde (VII).

An attempt to convert β-bromostyrene into styryl-lithium, and thence by reaction with crotonylideneacetone (IV) into (V), furnished a product similar in physical properties to (V) but giving on anionotropic rearrangement only minute amounts of the crystalline alcohol (VI). While the initial reaction product undoubtedly contained an appreciable quantity of the styryl-carbinol (V), it was probably contaminated with the corresponding phenylacetylenyl derivative. Wright (*J. Org. Chem.*, 1936, **1**, 459) has previously reported the formation of a mixture (4 : 1) of styryl-lithium and lithium phenylacetylide on reaction of β-bromostyrene with lithium. A similar mixture (5 : 1) of ethylenic and acetylenic derivatives has recently been observed in the corresponding reactions of *cis*-propenyl bromide (Braude and Coles, *J.*, in the press).



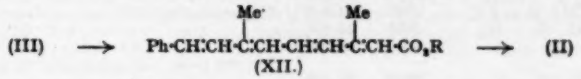
A convenient method has been developed for the synthesis of 3-methylocta-2 : 4 : 6-trienal (VII), which was required both in the present investigations and in connection with studies on the synthesis, from lithium *cyclo*hexenyls, of polyenes related to vitamin A (Braude, Bruun, Weedon, and Woods, forthcoming publication). A Reformatsky reaction of crotonylideneacetone (IV) with methyl bromoacetate leading to the triene-ester (VIII; R = Me) in 15% yield was reported by Kuhn and Hofer (*Ber.*, 1932, **65**, 651). The corresponding ethyl ester (VIII; R = Et) has now similarly been prepared in 60% yield after dehydration of the intermediate hydroxy-ester with toluene-*p*-sulphonic acid. Reduction of (VIII; R = Et) with lithium aluminium hydride furnished in 87% yield the triene-alcohol (IX) which was oxidised with manganese dioxide to the required aldehyde (VII) in 80% yield. Catalytic hydrogenation of (VII) gave 3-methyloctanal.

The aldehyde (VII) was also prepared, though less conveniently, by application of Arens and van Dorp's method (*Rec. Trav. chim.*, 1948, **67**, 973; cf. Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823) for the synthesis of αβ-unsaturated aldehydes. Ethoxyacetylenylmagnesium

bromide reacted with (IV) to give the alcohol (X) (44% yield), which on partial hydrogenation of the triple bond and subsequent treatment with dilute acid was converted into the aldehyde (VII).

Phenylmagnesium bromide and (VII) gave the alcohol (XI) as a crystalline solid. Treatment with 0·01M-hydrochloric acid caused anionotropic rearrangement to (VI), which was identical with the compound obtained by the alternative method and on oxidation gave (III).

A Reformatsky reaction of the ketone (III) and subsequent dehydration gave a mixture of unsaturated esters (XII; R = Et), one of which (A) was isolated as a crystalline solid. Hydrolysis of the ethyl esters furnished isomeric forms A and B, in 11 and 18% yields respectively (based on III), of the phenyl analogue (XII; R = H) of vitamin A acid. Since



these isomeric acids were both derived from the same crystalline ketone, which presumably possessed a *trans*-configuration about all three ethylenic bonds, they probably differ in geometrical configuration about the αβ-double bond. Isomerism of this type has recently been reported for vitamin A acid itself (Inhoffen, Bohlmann, and Bohlmann, *Annalen*, 1950, **568**, 47). The acids A and B yielded, with diazomethane, isomeric methyl esters (XII; R = Me), which on hydrolysis regenerated the parent acids.

Reduction of the crystalline ethyl ester (XII; R = Et) with lithium aluminium hydride, as described by Schwarzkopf *et al.* (*loc. cit.*) for vitamin A ester, furnished the crystalline phenyl analogue (II), m. p. 137°, of vitamin A, in 40% yield. This was characterised by oxidation with manganese dioxide to the corresponding aldehyde and conversion of the latter into the 2 : 4-dinitrophenylhydrazone.

The acids A and B were fed to young rats on a vitamin-A-deficient diet, as aqueous solutions (buffered to pH 10) of the potassium and sodium salts respectively. No growth responses were obtained in doses which would have revealed activity of the order of one-thousandth of that of vitamin A_1. The sodium salt of vitamin A_1 acid, when similarly tested, exhibits growth-promoting properties equal to those of the natural vitamin (Arens and van Dorp, *Nature*, 1946, **158**, 60).

The light-absorption properties of the compounds described in this paper are recorded in the Table. The phenyl analogues of vitamin A acid and vitamin A exhibit maximal absorption at wave-lengths intermediate between those of the corresponding vitamin A_1 and A_2 derivatives. More vibrational fine structure is apparent in the spectrum of (II) than in those of either vitamin A_1 or A_2.

Experimental.

Light-absorption data, the majority of which are recorded in the Table, were determined in alcohol unless otherwise stated.

All the operations were carried out in inert atmospheres.

The 2 : 4-dinitrophenylhydrazones were purified by chromatographic adsorption from benzene solutions on a column of alumina. All other chromatograms were performed on alumina which had been partially deactivated as described by Cheeseman, Heilbron, Jones, and Weedon (*J.*, 1949, 3120).

Manganese dioxide was selected from various commercial batches by comparing their activities in the oxidation of cinnamyl alcohol under the following conditions. A solution of crystalline cinnamyl alcohol (0·25 g.) in light petroleum (b. p. 40—60°; dried over sodium) (50 c.c.) was shaken for 2 hours at 20° with a sample (2·0 g.) of the manganese dioxide (dried over phosphoric oxide) under test. The mixture was then filtered, the filtrate evaporated, and the residue treated with an excess of 2 : 4-dinitrophenylhydrazine sulphate in methanol. The resulting precipitate was removed and crystallised from ethyl acetate, giving cinnamaldehyde 2 : 4-dinitrophenylhydrazone. Batches of manganese dioxide giving yields of *ca.* 0·35 g. were employed in subsequent oxidations. In a blank determination without manganese dioxide only a small amount (23 mg.) of the crude derivative was obtained (cf. Braude and Forbes, *J.*, in the press).

β-Bromostyrene was prepared by Nef's method (*Annalen*, 1899, **308**, 264; cf. Dufraisse, *Ann. Chim.*, 1922, **17**, 170) and had m. p. 6—7°, b. p. 106°/23 mm., n_D^{17} 1·6040.

Ethyl 2-Methylhepta-1 : 3 : 5-triene-1-carboxylate (VIII; R = Et) (With K. R. Bharucha).—About a quarter of a mixture of crotonylideneacetone (55 g.) and ethyl bromoacetate (90 g.; freshly distilled) was added to activated zinc wool (33 g.; cf. Fieser and Johnson, *J. Amer. Chem. Soc.*, 1940, **62**, 575) and benzene (150 c.c.). The mixture was heated under reflux until reaction commenced and then the remainder of the ketone–bromoacetate mixture added at such a rate that gentle refluxing was maintained. When the addition was complete (45 minutes), heating was recommenced and continued for 20 minutes.

The mixture was cooled and shaken with dilute acetic acid (1 l.; N.). Isolation of the product with benzene in the usual manner and distillation gave an oil (71 g.), b. p. 88—94°/0·5 mm., n_D^{21} 1·4800. Redistillation of a small portion gave the pure *hydroxy-ester* as a colourless oil, b. p. 83°/0·1 mm., n_D^{18} 1·4825 (Found: C, 67·0; H, 9·05. $C_{11}H_{16}O_3$ requires C, 66·65; H, 9·15%). Light absorption: maximum, 2280 Å; ε, 29,500.

A solution of the crude hydroxy-ester and toluene-*p*-sulphonic acid (0·48 g.) in benzene (1 l.) was heated under reflux for 6 hours, the water which separated during the first hour being removed. The solution was cooled, washed with saturated sodium hydrogen carbonate solution, dried, and evaporated. Distillation of the residue gave the *triene-ester* (53 g.) as a pale yellow oil b. p. 139—140°/18 mm., 107—108°/2 mm., 78°/0·5 mm., n_D^{21} 1·5600—1·5650 (mainly >1·5640) (Found: C, 73·3; H, 8·9. $C_{11}H_{14}O_2$ requires C, 73·3; H, 8·95%). Light absorption: see Table.

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
Triene-ester (VIII; R = Et) ...	2990	34,000
Triene-acid (VIII; R = H) ...	2960	42,000
	3020 *	38,000
Me·[CH:CH]$_3$·CO$_2$H [1]	2940	36,000
Triene-alcohol (IX)	2580 *	45,000
	2680	54,000
	2800	43,500
Me·[CH:CH]$_3$·CH$_2$·OH [2]	2560	42,500
	2645	53,000
	2780	46,500
Ethoxyacetylenic alcohol (X) ...	2280	20,000
Me·CH:CH·CH:CH·CMe(OH)·C:CH [3]	2270	26,500
Triene-aldehyde (VII)	3220	30,500
Me·[CH:CH]$_3$·CHO [1]	3160	37,000
Triene alcohol (XI)	2690	22,500
	2800	19,500
Styrylcarbinol (V)	2280	19,500
	2370	19,500
Triene-alcohol (VI)	3190	48,000
	3320	36,000
Ketone (III)	3600	42,000
Ethyl ester A (XII; R = Et)	3680	56,500
Methyl ester A (XII; R = Me)	3540 *	44,500
	3670	48,500
Methyl ester B (XII; R = Me)	3500 *	45,500
	3650	53,500
Acid A (XII; R = H)	3640	56,000
Acid B (XII; R = H)	3630	51,000
Vitamin A_1 acid [4]	3500	42,500
Vitamin A_2 acid [5]	3720	39,500
Phenyl-alcohol (II)	3300	46,500
	3430	50,500
	3620	45,000
Vitamin A_1 [6]	3280	49,000
Vitamin A_2 [5]	2880	19,000
	3520	37,500

* Inflexion.

[1] Hausser, Kuhn, Smakula, and Hoffer, *Z. physikal. Chem.*, 1935, **29**, *B*, 371. [2] Heilbron, Johnson, Jones, and Raphael, *J.*, 1943, 265. [3] Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, *J.*, 1949, 2031. [4] Wendler, Slates, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719. [5] Farrar, Hamlet, Henbest, and Jones, *Chem. and Ind.*, 1951, 49. [6] Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 1947, **30**, 1911.

Repetition of the Reformatsky reaction on twice the scale, and dehydration of the crude hydroxy-ester without prior distillation, gave the triene-ester in undiminished yield.

Ethyl 2-Methylheptane-1-carboxylate.—A solution of the above triene-ester (2·534 g.) in ethyl acetate (25 c.c.) was shaken in hydrogen in the presence of Adams's platinum catalyst until absorption was complete (hydrogen absorbed, 716 c.c. at 27°/759 mm., equiv. to 2·9 double bonds). Removal of catalyst and solvent, and distillation of the residue, gave the saturated *ester* (1·8 g.), b. p. 100—102°/18 mm., n_D^{24} 1·4236 (Found: C, 70·5; H, 11·85. $C_{11}H_{22}O_2$ requires C, 70·9; H, 11·9%).

2-Methylhepta-1 : 3 : 5-triene-1-carboxylic Acid.—A solution of the above triene-ester (2·0 g.) in methanolic potassium hydroxide (10% w/v; 12 c.c.) was heated under reflux for 45 minutes. After cooling, the mixture was poured into water (150 c.c.), and the non-hydrolysable portion extracted with ether. The aqueous solution was acidified (pH 4) with dilute (1 : 1) phosphoric acid, and the precipitated solid (1·33 g.), m. p. 95—115°, separated. Recrystallisation from benzene–methanol gave the acid (0·65 g.) as prismatic needles, m. p. 160—161° (Kuhn and Hoffer, *Ber.*, 1932, **65**, 651, give m. p. 160—161°). Light absorption: see Table.

3-Methylocta-2 : 4 : 6-trien-1-ol (IX).—A solution of the triene ester (VIII; R = Et) (45 g.) in ether (100 c.c.) was added dropwise to a stirred solution of lithium aluminium hydride (13·5 g.; *ca.* 80% pure) in ether (500 c.c.) at −40°. The temperature of the mixture was then allowed to rise to −20° and stirring continued for 1 hour at −20°. Ethyl acetate (28 c.c.) was added, to decompose the excess of hydride, and then a saturated solution of ammonium chloride (58 c.c.). The temperature of the mixture was allowed to rise to 20° and the mixture then filtered and the solid washed well with ether. The combined ethereal washings and filtrate were dried and evaporated. Distillation of the residue gave the *alcohol* (30 g.) as a colourless oil, b. p. 85°/0·8 mm., n_D^{27} 1·5656 (Found: C, 78·45; H, 10·25. $C_9H_{14}O$ requires C, 78·2; H, 10·2%). Light absorption: see Table. The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 80—100°) in yellow prisms, m. p. 124° (Found: N, 8·65. $C_{16}H_{16}O_6N_2$ requires N, 8·45%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 106° (Found: C, 77·7; H, 7·25. $C_{20}H_{21}O_2N$ requires C, 78·15; H, 6·9%).

1-Ethoxy-3-methylocta-4 : 6-dien-1-yn-3-ol (X).—Crotonylideneacetone (12·2 g.) in ether (50 c.c.) was added dropwise to an ice-cooled, stirred suspension of ethoxyacetylenylmagnesium bromide (from

3·0 g. of Mg and 10·0 g. of ethoxyacetylene, according to Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823) in ether (300 c.c.). After the mixture had been stirred at 0° for a further 20 minutes, the Grignard complex was decomposed by addition of a saturated aqueous solution of ammonium chloride, and the product then isolated in the usual manner. Distillation gave the *ethoxyacetylene-alcohol* (9·2 g.), b. p. 82°/0·3 mm., n_D^{20} 1·4920—1·4971 (Found: C, 73·85; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%). Light absorption: see Table.

3-*Methylocta*-2 : 4 : 6-*trienal* (VII).—(*a*) A solution of the triene-alcohol (IX) (24·8 g.) in light petroleum (b. p. 40—60°) (1250 c.c.) was shaken with manganese dioxide (120 g.) at 20° for 4 hours. The mixture was filtered and the filtrate was evaporated. Distillation of the residue gave the *aldehyde* (20·0 g.) as a pale yellow oil, b. p. 70—75°/0·1 mm., n_D^{24} 1·6005 (Found: C, 79·2; H, 9·15. $C_9H_{12}O$ requires C, 79·4; H, 8·9%). Light absorption: see Table. The 2 : 4-*dinitrophenylhydrazone*, crystallised from ethyl acetate, had m. p. 192—193° (Found: N, 17·7. $C_{15}H_{16}O_4N_4$ requires N, 17·7%). Light absorption in chloroform (main band only): maximum, 4050 Å; ε, 44,000. A portion (150 mg.) was converted into the *semicarbazone* which crystallised from aqueous methanol in pale yellow plates (195 mg.), m. p. 178—179° (decomp.), and decomposed rapidly even when kept at 0° (Found: C, 60·75; H, 10·55. $C_{10}H_{15}ON_3$ requires C, 60·25; H, 10·6%). Light absorption: maxima, 3250 and 3390 Å; ε, 36,500 and 33,000 respectively.

(*b*) A solution of the ethoxyacetylene-alcohol (X) (6·4 g.) in ethyl acetate (40 c.c.) was shaken in the presence of 1% palladium–calcium carbonate (0·5 g.) in an atmosphere of hydrogen. When one molar proportion (800 c.c. at 19°/765 mm.) of hydrogen had been absorbed the reaction was interrupted. After removal of catalyst and solvent the residue was distilled, giving an oil (2·8 g.), b. p. 64—65°/0·4 mm., n_D^{19} 1·5316. A portion (2·0 g.) of the latter was shaken in ether (10 c.c.) with 0·2N-sulphuric acid (20 c.c.) at 20° for 40 minutes. Isolation of the product as usual gave the aldehyde (1·2 g.), b. p. 63°/0·2 mm.; n_D^{21} 1·600. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate and had m. p. 191°, undepressed on admixture with the specimen described above. A portion (200 mg.) of the aldehyde was converted into the semicarbazone which crystallised from aqueous methanol in yellow plates (214 mg.), m. p. 179° (decomp.).

3-*Methyloctanal*.—The preceding aldehyde [3·7 g., from (*a*)] in methanol (20 c.c.) was shaken in an atmosphere of hydrogen, in the presence of platinic oxide, until absorption was complete (hydrogen absorbed, 1910 c.c. at 20°/749 mm., equiv. to 2·8 double bonds). After removal of catalyst and solvent the crude product was distilled giving 3-*methyloctanal* (2·13 g.), b. p. 79°/15 mm., n_D^{18} 1·4320 (Found: C, 76·05; H, 12·65. $C_9H_{18}O$ requires C, 76·0; H, 12·75%). The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in needles, m. p. 79—80° (Found: N, 17·5. $C_{15}H_{22}O_4N_4$ requires N, 17·4%). The *semicarbazone* crystallised from aqueous methanol in plates, m. p. 86° (Found: C, 60·25; H, 10·55; N, 21·3. $C_{10}H_{21}ON_3$ requires C, 60·25; H, 10·6; N, 21·1%).

3-*Methyl*-1-*phenylocta*-2 : 4 : 6-*trien*-1-*ol* (XI).—A solution of the triene-aldehyde (VII) (6·5 g.) in ether (50 c.c.) was added during 20 minutes to a stirred solution of phenylmagnesium bromide (from 2·4 g. of Mg) at 0°. Stirring was continued for a further hour at 20° and the complex was then decomposed by the addition of ammonium chloride (15 g.) in water (60 c.c.). The ethereal layer was separated, washed with water, dried ($MgSO_4$ + trace of K_2CO_3), and evaporated. The residual pale yellow oil (10·0 g.) was kept in light petroleum (b. p. 60—80°; 25 c.c.) at 0° for 40 hours. The solid which separated was recrystallised from the same solvent, giving the *alcohol* (3·3 g.) as colourless needles, m. p. 73° (Found: C, 83·75; H, 8·45. $C_{16}H_{18}O$ requires C, 84·05; H, 8·45%). Light absorption: see Table.

Evaporation of the mother-liquors and distillation of the residue gave a further quantity (4·3 g.), b. p. 80° (bath-temp.)/10^{-4} mm., n_D^{18} 1·5856, which solidified when seeded and had m. p. 70°.

3-*Methyl*-1-*phenylocta*-1 : 4 : 6-*trien*-3-*ol* (V).—A solution of crotonylideneacetone (49·5 g.; freshly distilled) in ether (200 c.c.) was added during 45 minutes to a filtered solution of styrylmagnesium bromide (prepared from 91·6 g. of β-bromostyrene and 36·5 g. of magnesium powder according to Gilman, *Rec. Trav. chim.*, 1935, **54**, 590) in ether (300 c.c.) at 0°. Stirring was continued for 30 minutes at 20°, and then a solution of ammonium chloride (150 g.) in water (500 c.c.) was added. The ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal solutions were washed with water and dried ($MgSO_4$ + trace of K_2CO_3). The solvent was removed, finally at 60°/0·2 mm. for ½ hour, the residue (80 g.) dissolved in light petroleum (b. p. 60—80°; 40 c.c.), and the solution kept at 0° for 12 hours. Diphenylbutadiene (4·3 g.) separated as plates, m. p. 136—137°, which after one crystallisation from the same solvent had m. p. 150—151° (Pinckard, Wille, and Zechmeister, *J. Amer. Chem. Soc.*, 1948, **70**, 1938, give m. p. 152—153°). The mother-liquors were evaporated. Distillation of a small portion (1·0 g.) of the residue gave the tertiary *alcohol* (0·65 g.) as a viscous oil, b. p. 85° (bath-temp.)/10^{-4} mm., n_D^{25} 1·5743 (Found: C, 84·15; H, 8·55%). Light absorption: see Table. The majority of the crude product was used for the preparation of (VI) without further purification.

An attempt to convert β-bromostyrene into styryl-lithium (cf. Wright, *J. Org. Chem.*, 1936, **1**, 459) and thence by reaction with crotonylideneacetone into the required tertiary carbinol (V) gave in good yield an oil, b. p. 120° (bath-temp.)/10^{-3} mm., n_D^{20} 1·5745 (Found: C, 84·25; H, 8·45%). Light absorption: maxima, 2280, 2370, and 2420 Å; $E_{1\,cm.}^{1\%}$, 1120, 1100, and 1180 respectively. Anionotropic rearrangement of this product in the manner described below for (V) gave only traces of the crystalline carbinol (VI).

6-*Methyl*-8-*phenylocta*-3 : 5 : 7-*trien*-2-*ol* (VI).—(*a*) 3-Methyl-1-phenylocta-2 : 4 : 6-trien-1-ol (6·0 g.; m. p. 71°) was dissolved in a 0·01M-solution of hydrochloric acid in water (160 c.c.)–acetone (240 c.c.), and the resulting solution kept at 20° overnight. A saturated solution of sodium hydrogen carbonate was added until the pH of the mixture rose to 7—8. The bulk of the acetone was then removed under reduced pressure and the product (5·5 g.) isolated with ether in the usual way. Light absorption: maxima, 2690, 2800, 3190, and 3300 Å; $E_{1\,cm.}^{1\%}$, 840, 840, 1090, and 700 respectively. Recrystallisation from light

petroleum (b. p. 60—80°) gave *6-methyl-8-phenylocta-3 : 5 : 7-trien-2-ol* (1·95 g.) as colourless prisms, m. p. 102·5° (Found : C, 83·75; H, 8·55. $C_{15}H_{18}O$ requires C, 84·05; H, 8·45%). Light absorption : see Table.

(*b*) The crude tertiary carbinol (V) (50 g.) was dissolved in a 0·01M-solution of hydrochloric acid in water (540 c.c.)–acetone (1260 c.c.), and the solution kept at 20° for 60 hours. The product, isolated as described in (*a*), was an oil (48·7 g.), n_D^{21} 1·6170. Light absorption : maxima, 3180 and 3280 Å; $E_{1\,cm.}^{1\%}$ 950 and 800 respectively.

Trituration of the crude product with light petroleum (b. p. 60—80°) gave a solid which on recrystallisation from the same solvent yielded 6-methyl-8-phenylocta-3 : 5 : 7-trien-2-ol (15·0 g.), m. p. 103°, undepressed on admixture with a specimen from (*a*). Attempts to isolate further quantities of the crystalline alcohol by evaporation of the mother-liquors and chromatography of the residual oil (32 g.) were unsuccessful.

When a solution of the crystalline alcohol (523 mg.) in ethyl acetate (15 c.c.) was shaken in hydrogen and in the presence of a platinum catalyst (30 mg.), 179 c.c. of hydrogen were adsorbed at 21·5°/761 mm., equiv. to 2·95 double bonds.

6-Methyl-8-phenylocta-3 : 5 : 7-trien-2-one (III).—A solution of the preceding alcohol [10·0 *g.*; m. p. 101°, prepared by method (*b*)] in light petroleum (b. p. 40—60°; 900 c.c.) was shaken with manganese dioxide (90 g.) at 20° for 5 hours. The mixture was filtered and the filtrate evaporated, giving a solid (10·0 g.) which on recrystallisation from light petroleum (b. p. 60—80°) yielded the *ketone* (7·7 g.) as yellow plates, m. p. 102°, depressed to 83—89° on admixture with the parent alcohol (Found : C, 84·45; H, 7·55. $C_{15}H_{16}O$ requires C, 84·85; H, 7·6%). Light absorption : see Table. The *2 : 4-dinitrophenylhydrazone* crystallised from ethyl acetate and had m. p. 192° (Found : N, 15·2. $C_{21}H_{20}O_4N_4$ requires N, 15·45%). Light absorption in chloroform (main band only) : maximum 4130 Å; ε, 33,500.

A specimen of the ketone prepared by oxidation of the alcohol from (*a*) had m. p. 100°, undepressed on admixture with the specimen described above. It yielded a 2 : 4-dinitrophenylhydrazone, m. p. 191°, undepressed on admixture with the specimen described above.

2 : 6-Dimethyl-8-phenylocta-1 : 3 : 5 : 7-tetraene-1-carboxylic Acids (XII; R_4 = H).—A solution of the preceding ketone (5·0 g.) and ethyl bromoacetate (4·4 g.; freshly distilled) in benzene (15 c.c.) was added dropwise to a mixture of activated zinc (1·7 g.; cf. Fieser and Johnson, *loc. cit.*), benzene (45 c.c.), and a trace of iodine. When about one-fifth of the ketone solution had been added, the mixture was refluxed until reaction commenced (15 minutes), and then the remainder of the ketone solution added at such a rate as to maintain a gentle reflux. The mixture was heated under reflux for a further ½ hour—all the zinc had by then reacted—cooled, and shaken with 5% acetic acid (150 c.c.). The benzene layer was separated, washed well with sodium hydrogen carbonate solution, and dried ($MgSO_4$).

The resulting solution of hydroxy- and unsaturated esters was diluted to *ca.* 150 c.c. with benzene, toluene-*p*-sulphonic acid (30 mg.) was added, and the mixture heated under reflux for 5 hours (the water which separated during the first ½ hour was removed by azeotropic distillation with benzene). The benzene solution was cooled, washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated, giving a red oil (6·0 g.), n_D^{23} 1·675. This was dissolved in light petroleum (b. p. 40—60°) (8 c.c.), and the solution was poured on to a column of partially deactivated alumina (350 g.; Grade IV; cf. Brockmann and Schodder, *Ber.*, 1941, **74**, 73). The chromatogram was developed with the same solvent and the least strongly adsorbed band eluted. Evaporation of the solvent gave a yellow oil (4·2 g.), n_D^{23} 1·671, which exhibited a light-absorption maximum at 3680 Å; $E_{1\,cm.}^{1\%}$, 1270. On storage of a solution of the oil in light petroleum (b. p. 60—80°) at 0° for a few hours, a solid separated which was recrystallised from benzene and from ether, giving *ethyl 2 : 6-dimethyl-8-phenylocta-1 : 3 : 5 : 7-tetraene-1-carboxylate* (ethyl ester A) (1·07 g.) as yellow needles, m. p. 122—123° (Found : C, 80·75; H, 8·0. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%). Light absorption : see Table. Evaporation of the mother-liquors gave a crude ester as an oil (3·1 g.).

A solution of the crystalline ethyl ester (0·3 g.; m. p. 121°) in methanolic potassium hydroxide (10% w/v; 7 c.c.) was warmed for 1 hour at 60° and then cooled. The potassium salt (216 mg.) crystallised and was separated and washed with methanol. The potassium salt was dissolved in water (20 c.c.), and the solution acidified with phosphoric acid. The solid which separated was recrystallised from benzene giving the *acid A* (132 mg.) as yellow plates, m. p. 195° (Found : C, 80·25; H, 7·15. $C_{17}H_{18}O_2$ requires C, 80·45; H, 7·15%). Light absorption : see Table. The methanolic mother-liquors were diluted with water, and the non-hydrolysable material was extracted with ether. Acidification of the aqueous solution gave a further quantity (52 mg.) of acid A.

A solution of the crude liquid ethyl ester (3·1 g.) in methanolic potassium hydroxide (10% w/v; 45 c.c.) was kept at 20° for 54 hours. Isolation of the acidic product in the usual manner gave a solid (1·86 g.), m. p. 151—154°, which was recrystallised from 1 : 3 benzene–light petroleum (b. p. 60—80°), yielding *acid B* (1·085 g.) as yellow plates, m. p. 165° which was depressed on admixture with acid A (Found : C, 80·25; H, 7·35%). Light absorption : see Table. Acid B was also prepared in a subsequent experiment by hydrolysing the crude liquid ester at 60° for 1 hour.

Methyl 2 : 6-Dimethyl-8-phenylocta-1 : 3 : 5 : 7-tetraene-1-carboxylates (XII; R = Me).—A solution of acid A (140 mg.; m. p. 195°) in ether (10 c.c.) was treated at 0° with ethereal diazomethane (50% excess; standardised against benzoic acid). After 5 minutes at 0° the mixture was warmed to 30° to expel the excess of diazomethane, and the solvent was then removed under reduced pressure. The solid residue was dissolved in benzene (3 c.c.) and the solution poured on to a column of alumina (10 g.; Grade IV). The chromatogram was developed with light petroleum (b. p. 40—60°), and the single yellow band eluted. Evaporation of the solvent and crystallisation of the residue from 1 : 3 benzene–

light petroleum (b. p. 60—80°) gave the *methyl ester A* (114 mg.) as yellow needles, m. p. 125° (Found: C, 80·35; H, 7·55. $C_{18}H_{30}O_2$ requires C, 80·55; H, 7·5%). Light absorption: see Table.

Hydrolysis of a portion (73 mg.) of the ester by heating it under reflux with methanolic potassium hydroxide (10% w/v; 3 c.c.) and isolation of the acidic product in the usual manner gave acid A (51 mg.), m. p. 192°, undepressed on admixture with an authentic specimen.

Esterification of acid B (200 mg.; m. p. 162°) as described for the isomeric material gave a crude oil (210 mg.) which was dissolved in light petroleum (b. p. 40—60°) (10 c.c.). The solution was poured on to a column of alumina (30 g.; Grade IV). The chromatogram was developed with the same solvent and the single yellow band was eluted. Evaporation of the solvent and crystallisation of the residue from light petroleum (b. p. 60—80°) gave the *methyl ester B* (107 mg.) as pale yellow needles, m. p. 123° (Found: C, 80·7; H, 7·55%). Light absorption: see Table. A mixture of the two isomeric methyl esters had m. p. 121°.

The methyl ester B (200 mg.) was hydrolysed in the usual manner by boiling methanolic potassium hydroxide (10% w/v; 6 c.c.) for 1 hour and gave a crude acid (138 mg.), m. p. 143°, which was crystallised from 1 : 3 benzene–light petroleum (b. p. 60—80°), yielding acid B, m. p. 163°, undepressed on admixture with an authentic specimen.

3 : 7-*Dimethyl*-9-*phenylnona*-2 : 4 : 6 : 8-*tetraen*-1-*ol* (II).—A solution of the crystalline ethyl ester (560 mg.; m. p. 122—123°) of acid A in ether (25 c.c.) was added during 10 minutes to a stirred ethereal solution of lithium aluminium hydride (1·87% w/v; 9·5 c.c.) at −30°. The temperature of the mixture was allowed to rise to −15° (15 minutes) and stirring continued for a further ½ hour. Ethyl acetate (0·5 c.c.) was added and then saturated aqueous ammonium chloride (1 c.c.). The mixture was filtered and the filtrate dried and evaporated. The residual solid was crystallised from benzene–light petroleum (b. p. 60—80°), giving the *alcohol* (196 mg.) as pale yellow plates, m. p. 137° (Found: C, 85·35; H, 8·35. $C_{17}H_{22}O$ requires C, 85·15; H, 8·4%). Light absorption: see Table. Attempts to isolate further quantities of the pure alcohol by evaporation of the mother-liquors and chromatography of the residue were unsuccessful.

A solution of the crystalline material (33 mg.) in light petroleum (b. p. 40—60°; 7 c.c.) and benzene (2 c.c.) was shaken with manganese dioxide (300 mg.) for 4 hours. The mixture was filtered, the solid washed with benzene, and the combined filtrate and washings were evaporated. The residue was converted into the 2 : 4-*dinitrophenylhydrazone* which crystallised from 1 : 1 ethyl acetate–methanol and had m. p. 213—214° (Found: N, 13·1. $C_{23}H_{26}O_4N_4$ requires N, 13·4%). Light absorption in chloroform (main band only): maximum, 4400 Å; ε, 49,000.

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598. *The Synthesis of Long-chain Aliphatic Acids from Acetylenic Compounds. Part V.* The Synthesis of* trans-cis-*Herculin.*

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Catalytic partial hydrogenation of tetrolaldehyde diethyl acetal furnishes *cis*-crotonaldehyde diethyl acetal, which, on acid hydrolysis, yields *trans*-crotonaldehyde, characterised by conversion into *trans*-crotonic acid. Extension of this method of geometrical inversion has resulted in the synthesis of *trans-cis*-herculin; the product was not identical with natural herculin.

THE production of practically pure *cis*-ethylenic compounds by catalytic partial hydrogenation of the corresponding acetylenic derivatives (for discussion and references see Part I, *J.*, 1950, 115) suggested the employment of this method for the preparation of the hitherto unknown *cis*-crotonaldehyde. Tetrolaldehyde diethyl acetal (3 : 3-diethoxypropyne) smoothly absorbed one mol. of hydrogen under the influence of a palladium–calcium carbonate catalyst, to give a good yield of *cis*-crotonaldehyde diethyl acetal. Hydrolysis of this derivative with hot aqueous oxalic acid gave a product indistinguishable from ordinary (*trans*-)crotonaldehyde; this was confirmed by the preparation of its semicarbazone and 2 : 4-dinitrophenylhydrazone

* Part IV, *J.*, 1950, 2725.

and by its oxidation to *trans*-crotonic acid by means of silver oxide (Delepine and Bonnet, *Bull. Soc. chim.*, 1909, **5**, 883). The ready conversion of the initially-formed labile *cis*-aldehyde into the stable *trans*-isomer may be regarded as an acid-catalysed reaction proceeding through the intermediary of a mesomeric conjugate acid:

$$CH_3\cdot\overset{cis}{C}H{:}CH\cdot CHO + H^+ \longrightarrow CH_3\cdot\overset{+}{C}H{=}CH{=}CH\cdot OH \longrightarrow CH_3\cdot\overset{trans}{C}H{:}CH\cdot CHO + H^+$$

A similar intermediate has been postulated in the acid-catalysed bromination of αβ-unsaturated aldehydes (de la Mare and Robertson, *J.*, 1950, 2840).

In view of the ease and completeness of this geometrical inversion it was obviously of interest to extend its application to the preparation of the *iso*butylamide of undeca-1(*trans*) : 7-(*cis*)-diene-1-carboxylic acid (*trans-cis*-herculin) for comparison with the naturally-occurring insecticide herculin (cf. Part I for the synthesis of the *cis-cis*-isomer). The Grignard complex

$$\underset{(I)}{Pr^n\cdot C{:}C\cdot[CH_2]_4\cdot C{:}CH} \longrightarrow \underset{(II)}{Pr^n\cdot C{:}C\cdot[CH_2]_4\cdot C{:}C\cdot CH(OEt)_2} \xrightarrow[H_2]{Pd-}$$

$$\underset{(III)}{Pr^n\cdot\overset{cis}{C}H{:}CH\cdot[CH_2]_4\cdot\overset{cis}{C}H{:}CH\cdot CH(OEt)_2} \xrightarrow{H+} \underset{(IV)}{Pr^n\cdot\overset{cis}{C}H{:}CH\cdot[CH_2]_4\cdot\overset{trans}{C}H{:}CH\cdot CHO} \xrightarrow{Ag_2O}$$

$$\text{(V)}\quad Pr^n\cdot\overset{cis}{C}H{:}CH\cdot[CH_2]_4\cdot\overset{trans}{C}H{:}CH\cdot CO_2H \xrightarrow[2,\ NH_2Bu^i]{1,\ (COCl)_2} Pr^n\cdot\overset{cis}{C}H{:}CH\cdot[CH_2]_4\cdot\overset{trans}{C}H{:}CH\cdot CO\cdot NHBu^i \quad \text{(VI)}$$

derived from undeca-1 : 7-diyne (I; cf. Part I) reacted readily with ethyl orthoformate to give the diacetylenic acetal (II). The free aldehyde, prepared by hydrolysis of (II) with aqueous oxalic acid, condensed with semicarbazide acetate to give a derivative which, in view of its low melting point and solubility in light petroleum was probably not the expected semicarbazone but the corresponding isomeric pyrazole formed by intramolecular cyclisation. Partial catalytic hydrogenation of the diacetylenic acetal (II) employing palladium–calcium carbonate as catalyst resulted in the smooth absorption of two mols. of hydrogen to form the *cis-cis*-diethylenic acetal (III). Distillation of (III) in steam in the presence of oxalic acid led to hydrolysis of the acetal followed by the above-described geometrical inversion at the αβ-double bond only to form the *trans-cis*-aldehyde (IV). Silver oxide oxidation of this aldehyde to the corresponding *trans-cis*-acid (V) followed by already-described procedures of acid chloride formation and reaction with *iso*butylamine (cf. Part I) gave *trans-cis*-herculin (VI). This structure was confirmed by complete hydrogenation to the crystalline *N-iso*butyl-lauramide and by potassium permanganate oxidation to butyric, adipic, and *N-iso*butyloxamic acids.

Unlike the naturally occurring herculin (m. p. 59—60°) the above synthetic product was a liquid and possessed none of the physiological properties (burning taste, production of salivation) described for the natural product (Jacobson, *J. Amer. Chem. Soc.*, 1948, **70**, 4234). Again, in contrast to the ready deterioration on storage exhibited by natural herculin and its parent acid the above corresponding synthetic isomers were perfectly stable. Natural herculin must therefore be either the 1(*trans*) : 7(*trans*)- or 1(*cis*) : 7(*trans*)-isomer of (VI), and the synthesis of both these compounds is now under investigation.

Experimental.

Attempted Preparation of cis-*Crotonaldehyde.*—A solution of tetrolaldehyde diethyl acetal (3 : 3-diethoxypropyne) (7·45 g.; cf. Lunt and Sondheimer, *J.*, 1950, 3364) in ethyl acetate (50 c.c.) was stirred under hydrogen with palladium–calcium carbonate (10%; 500 mg.) until 1 mol. of hydrogen had been absorbed. The catalyst was filtered off and the solvent evaporated off through a column; distillation of the residue gave cis-*crotonaldehyde diethyl acetal* (5·2 g.), b. p. 144—146°/757 mm., n_D^{18} 1·4170 (Found: C, 66·1; H, 10·8. $C_8H_{14}O_2$ requires C, 66·6; H, 11·2%). A mixture of the *cis*-acetal (9·7 g.), oxalic acid (5 g.), and water (50 c.c.) was distilled in steam until the distillate gave only a faint precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate. The steam-distillate was saturated with salt and constantly extracted with ether; drying ($MgSO_4$) and evaporation gave a pale yellow oil (3·2 g.) with the acrid smell of crotonaldehyde. The 2 : 4-dinitrophenylhydrazone (scarlet needles, m. p. 191°, from ethanol) and semicarbazone (plates, m. p. 202—204°, from ethanol) made from this product showed no depression in m. p. on admixture with the corresponding derivatives of *trans*-crotonaldehyde; distillation gave a liquid with b. p. 102—104°, n_D^{18} 1·4368 (Enklaar, *Ber.*, 1916, **49**, 211, gives b. p. 102·2—102·5°, n_D^{20} 1·43620, for pure *trans*-crotonaldehyde).

A solution of the product (1·6 g.) in ethanol (25 c.c.) was mixed with a solution of silver nitrate (7·6 g.) in water (25 c.c.) and sodium hydroxide solution (39 c.c.; N.) was added slowly with stirring. After 16 hours at room temperature the precipitated silver was filtered off and washed with water,

The ethanol was removed by heating the combined filtrates under reduced pressure and the resulting aqueous solution freed from non-acidic impurities by extraction with ether. The aqueous layer was acidified with dilute sulphuric acid and constantly extracted with ether; drying ($MgSO_4$) and evaporation of the solvent gave an oil which rapidly solidified. Crystallisation of this product from light petroleum (b. p. 60—80°) gave blades (960 mg.), m. p. 71—72° undepressed on admixture with authentic *trans*-crotonic acid (m. p. 71—72°).

Dodeca-2 : 8-*diyn*-1-*al Diethyl Acetal* (1 : 1-*Diethoxydodeca*-2 : 8-*diyne*) (II).—To a solution of ethylmagnesium bromide [from magnesium (3 g.), ethyl bromide (20 g.), and ether (200 c.c.)] was added a solution of undeca-1 : 7-diyne (17 g.) in ether (20 c.c.), and the mixture heated under reflux until the evolution of ethane had ceased. A solution of ethyl orthoformate (18 g.) in ether (20 c.c.) was then rapidly run in and the mixture heated under reflux for a further 6 hours. The cooled reaction mixture was hydrolysed with cold 50% acetic acid, and the separated ethereal layer washed with sodium hydrogen carbonate solution and water. Drying ($MgSO_4$), evaporation, and distillation under reduced pressure gave a small fore-run (1·3 g.) of unchanged diyne, followed by the diacetylenic *acetal* (21·6 g., 82%), a mobile, odorous liquid, b. p. 115—116°/0·2 mm., n_D^{18} 1·4640 (Found: C, 76·7; H, 10·2. $C_{16}H_{26}O_2$ requires C, 76·8; H, 10·45%).

A small sample of the acetal was distilled in steam in the presence of oxalic acid. The free aldehyde, isolated by means of ether from the steam-distillate, was treated with alcoholic semicarbazide acetate. After dilution of the solution with water the turbid reaction mixture slowly deposited needles, m. p. 71—72° after crystallisation from light petroleum (b. p. 60—80°) (Found: C, 66·8; H, 8·3; N, 18·25. $C_{13}H_{19}ON_3$ requires C, 66·9; H, 8·2; N, 18·0%).

Dodeca-2(cis) : 8(cis)-*dien*-1-*al Diethyl Acetal* [1 : 1-*Diethoxydodeca*-2(cis) : 8(cis)-*diene*] (III).—A solution of the diacetylenic acetal (II) (10·03 g.) in ethyl acetate (50 c.c.) was stirred under hydrogen with palladium–calcium carbonate (10%; 500 mg.) until 2 mols. of hydrogen had been absorbed (1945 c.c. at 18°/764·5 mm.). Removal of catalyst and solvent, followed by distillation, gave the *cis* : *cis*-diene *acetal* (9·3 g.) as a mobile odorous liquid, b. p. 84—85°/0·1 mm., n_D^{18} 1·4490 (Found: C, 75·55; H, 11·4. $C_{16}H_{30}O_2$ requires C, 75·55; H, 11·9%).

N-iso*Butylundeca*-1(trans) : 7(cis)-*diene*-1-*carboxyamide* (trans-cis-*Herculin*) (VI).—A mixture of the diene acetal (5 g.), oxalic acid (5 g.), and water (50 c.c.) was distilled in steam until no more oily drops appeared in the condensate. Isolation by means of ether gave the *trans-cis*-aldehyde (IV); the *semicarbazone*, prepared in the usual manner, crystallised in plates, m. p. 162°, from ethanol (Found: N, 17·8. $C_{12}H_{23}ON_3$ requires N, 17·7%).

A solution of the crude, undistilled aldehyde (2·2 g.) in ethanol (45 c.c.) was mixed with a solution of silver nitrate (2 g.) in water (4 c.c.), and sodium hydroxide solution (19 c.c.; N.) was added slowly. After 16 hours at room temperature the reaction mixture was worked up as described for the above cognate preparation. Distillation of the product gave *undeca*-1(trans) : 7(cis)-*diene*-1-*carboxylic acid* (1·6 g.), b. p. 98—100°/10^{-6} mm., n_D^{20} 1·4710 (Found: C, 73·2; H, 10·3. $C_{12}H_{20}O_2$ requires C, 73·45; H, 10·3%). The S-*benzylthiuronium* salt crystallised from aqueous alcohol or ethyl acetate in prismatic plates, m. p. 143—144° (Found: N, 7·7. $C_{20}H_{32}O_2N_2S$ requires N, 7·75%).

The diethylenic acid (1·5 g.), oxalyl chloride (4 g.), and benzene (10 c.c.) were heated under reflux for 45 minutes, the benzene and excess of acid chloride were removed under reduced pressure, more benzene was added, and the solution again taken to dryness. The resulting crude acid chloride was dissolved in ether (10 c.c.) and treated slowly with a solution of *iso*butylamine (5 g.) with ice-cooling and continuous shaking. After 1 hour at room temperature the ethereal solution was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water and dried ($MgSO_4$). Evaporation and distillation gave trans-cis-*herculin* (1·3 g.) as a colourless liquid, b. p. 133—135°/10^{-6} mm., n_D^{19} 1·4810 (Found: C, 76·3; H, 11·3; N, 5·8. $C_{16}H_{29}ON$ requires C, 76·45; H, 11·65; N, 5·55%).

Complete hydrogenation of *trans-cis*-herculin gave N-*iso*butyl-lauramide, m. p. and mixed m. p. 51—52°. Permanganate oxidation gave the expected fission fragments, butyric, adipic, and *N*-*iso*-butyloxamic acids, in yields similar to those obtained for the natural product and the *cis-cis*-isomer (Part I).

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599. *The Chemistry of the Triterpenes. Part IX.* Elucidation of the Betulin–Oleanolic Acid Relationship.*

By G. S. Davy, T. G. Halsall, and E. R. H. Jones.

The inter-relation of the lupeol and the β-amyrin series of triterpenes has again been demonstrated. Betulonic acid is converted into a saturated keto-lactone by isomerisation with acidic reagents. Reduction of this lactone with lithium aluminium hydride gives a triol, acetylation of which is accompanied by dehydration giving the diacetate of moradiol. The relation of this diol to germanicol and oleanolic acid has been elucidated by Barton and Brooks (*J.*, 1951, 257), and hence a relation between betulin and oleanolic acid is established. It is therefore confirmed that β-amyrin, germanicol, and lupeol are identical in rings A, B, C, and D, except for the presence of a double bond in ring C in β-amyrin (cf. Ames, Halsall, and Jones, *J.*, 1951, 450); further, it can now be concluded that the primary alcohol group of betulin and the carboxyl group of oleanolic acid occupy the same position relative to their pentacyclic ring systems.

Conversion of the carboxyl groups of betulinic acid and oleanolic acid into acetyl groups, and isomerisations of the resulting products under acidic conditions, are described.

A review of the lactonisation of betulinic acid indicated some anomalies which have been investigated and resolved. A preliminary account of part of this work has already been published (Davy, Halsall, and Jones, *Chem. and Ind.*, 1950, 732).

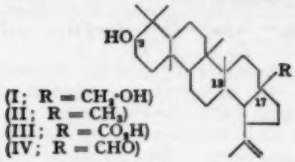
In continuation of our investigations (cf. Ames, Halsall, and Jones, *J.*, 1951, 450) on the inter-relation of the major groups of triterpenes and the members thereof, it was desirable to establish the relation between betulin (probably I), a triterpene of the lupeol group, and oleanolic acid (V), a member of the β-amyrin group of established structure. There would then follow a proof that the primary alcohol group of betulin occupies the same position relative to rings A, B, C, and D as the carboxyl group of oleanolic acid. Conversion of the primary alcohol group of betulin into a methyl group yields lupeol (Ruzicka and Brenner, *Helv. Chim. Acta*, 1939, **22**, 1532). Hence betulin differs from lupeol only in having one of the six methyl groups in the now established structure (Ames, Halsall and Jones, *loc. cit.*) replaced by a $-CH_2\cdot OH$ group. Some evidence for the position of the $-CH_2\cdot OH$ group relative to the *iso*propenyl side chain has already been provided by Ruzicka and Rey (*Helv. Chim. Acta*, 1943, **26**, 2143) who showed that the acetate of the betulin degradation product, bisnorlupanoldicarboxylic acid, formed an anhydride. This evidence, on the basis of the known structure of lupeol, suggests that the primary alcohol group of betulin is at $C_{(17)}$. Final proof of this is provided by the results described in this paper.

In establishing the inter-relation of lupeol (II) and β-amyrin (VI), both substances were converted *via* the corresponding ketones, β-amyrenone and lupenone, or the corresponding hydrocarbons, into δ-amyrene (VIII), or a derivative thereof, by isomerisation with acidic reagents. Similar isomerisation of betulin, provided that the hydroxyl groups remained intact and unreactive throughout the isomerisation, would yield δ-erythrodiol (IX), which could be obtained either by isomerisation of erythrodiol (VII) or by reduction of δ-oleanolic acid (Barton and Brooks, *loc. cit.*). However, treatment of betulin with formic acid leads to the production of the saturated cyclic ether, *allo*betulin (see following paper). Because of this, and the general unsuitability of triterpene alcohols for such isomerisation reactions (cf. Ames, Halsall, and Jones, *loc. cit.*), no attempt was made to isomerise betulin itself. Instead, attention was turned to betulinic acid (III), the acid obtained by the oxidation of the primary alcohol group of betulin, and to the corresponding ketone, betulonic acid. Robertson, Soliman, and Owen (*J.*, 1939, 1267) have already reported that betulinic acid is converted by hydrogen bromide in acetic acid into a saturated hydroxy-lactone, designated "lactone-A."

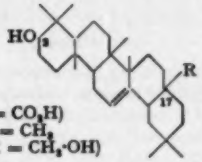
With sulphuric acid in acetic acid–benzene, methyl betulonate similarly gave a saturated keto-lactone, also obtained by chromic acid oxidation of "lactone-A." Treatment of the keto-lactone with lithium aluminium hydride resulted in the reductive scission of the lactone giving

* Part VIII, *J.*, 1951, 458.

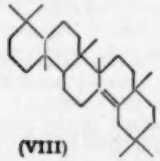
a triol, the $C_{(3)}$-keto-group also being reduced. One effect of this fission is thus to convert the lactonic carbonyl group, *i.e.*, the carboxyl group of the original betulonic acid, into a primary alcohol group (–O–CO– ⟶ –OH HO·CH_2–). Acetylation of the triol with acetic anhydride in pyridine gave a diacetate. Since betulin also forms a diacetate under these conditions,



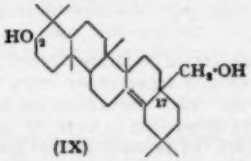
(I; R = CH_2·OH)
(II; R = CH_3)
(III; R = CO_2H)
(IV; R = CHO)



(V; R = CO_2H)
(VI; R = CH_3)
(VII; R = CH_2·OH)

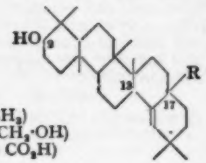


(VIII)

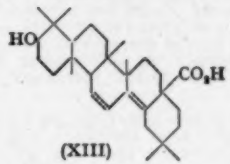


(IX)

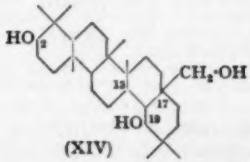
the two acetyl groups may be allocated to the secondary hydroxyl group at $C_{(3)}$ and the primary hydroxyl group, the new hydroxyl group resulting from the lactone fission being unreactive. Acetylation with acetic anhydride and pyridine under reflux gave a mixture of the diacetate and a triacetate. Acetic anhydride with boron trifluoride as catalyst also gave the triacetate, together with the diacetate of a mono-unsaturated diol formed apparently by dehydration involving the unreactive hydroxyl group. This diacetate proved to be that of moradiol (XI),



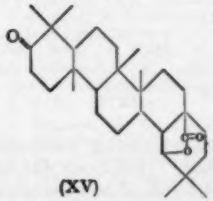
(X; R = CH_3)
(XI; R = CH_2·OH)
(XII; R = CO_2H)



(XIII)



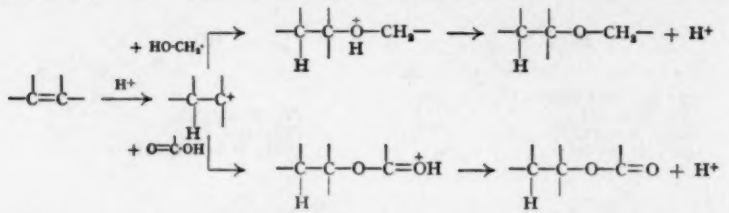
(XIV)



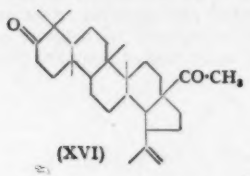
(XV)

belonging to the germanicol (X) group of triterpenes (Barton and Brooks, *loc. cit.*). The identity of the deacetylation product with an authentic sample of moradiol, kindly provided by Dr. D. H. R. Barton, was confirmed by a mixed melting-point determination. Barton and Brooks (*loc. cit.*) obtained moradiol by lithium aluminium hydride reduction of morolic acid which was most elegantly and completely demonstrated, partly by conversion into dehydro-oleanolic acid (XIII), to have structure (XII). The carboxyl group of oleanolic acid is therefore located at the same position ($C_{(17)}$) relative to the ring system as the primary alcohol group of moradiol. This group in the moradiol obtained from the lactone is derived from the carboxyl group of betulinic acid and hence the primary alcohol group of betulin. Consequently this group and the carboxyl group of oleanolic acid (V) occupy the same position relative to the pentacyclic system, and further confirmation of the common carbon skeleton and stereochemistry of rings A, B, and C in β-amyrin (VI), lupeol (II), and germanicol (X) is provided. The identity of the stereochemical configuration at $C_{(18)}$ in lupeol (II) and germanicol (X) is also proved.

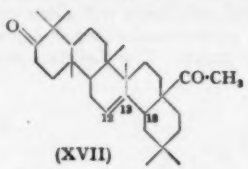
If it is assumed that no rearrangement occurs on dehydration of the triol, it can be assigned structure (XIV), proof of which and its implications are discussed in the following paper. The proof is unnecessary for the logical development of the arguments presented in this paper. Structure (XIV) for the triol leads to (XV) for the keto-lactone.



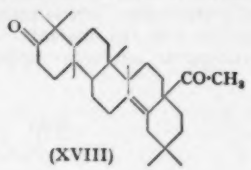
The formation of the saturated ether from betulin, and of the saturated lactone from betulonic acid, can be regarded as being interaction of the primary alcohol and carboxyl groups respectively with a carbonium ion formed under the acidic conditions. Inspection of these formulæ indicated that in order to proceed from the betulin to the δ-amyrin series by acidic isomerisation the primary alcohol group of betulin would have to be modified in some way other than by conversion into a carboxyl group or a derivative. Transformation of the carboxyl group of betulonic acid into an acetyl group and isomerisation of the resulting homolupenedione (XVI) appeared to offer a way out of this difficulty. For comparative



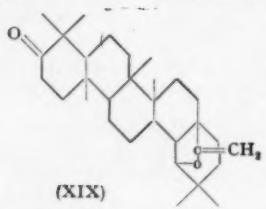
(XVI)



(XVII)



(XVIII)



(XIX)

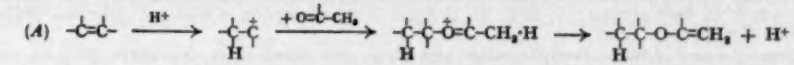
(XX)

purposes the corresponding homo-dione, homo-oleanenedione (XVII), was prepared by standard reactions. This dione was isomerised by sulphuric acid in acetic acid to the corresponding δ-compound, δ-homo-oleanenedione (XVIII). The absorption spectrum of this compound showed the presence of the two keto-groups and confirmed that the double bond had moved from the 12 : 13- to the 13 : 18-position (the use of ultra-violet light absorption data for the determination of double bond environment will be dealt with in forthcoming publications from these laboratories).

The homolupenedione was prepared in two ways. The first method used was that employed for the preparation of homo-oleanenedione. In the second the acetate of betulinaldehyde (IV) was treated with methyl-lithium, giving homolupenediol, oxidised to the dione (XVI).

The homolupenedione was then treated with 20% sulphuric acid in acetic acid. The same product was obtained whether the reaction solution was worked up after a shorter or longer time. The absorption spectrum of the isomerisation product indicated the presence of *only one* keto-group but also a double bond. Unsaturation was also indicated by a yellow colour with tetranitromethane. These data are only compatible with the formation of a cyclic vinyl ether which, in view of the structure put forward for the keto-lactone (XV), was formulated as (XIX) (cf. *A*). Support for this formulation was forthcoming from the absorption spectrum of tetrahydro-2-methylenefuran (XX) (Eglinton, Jones, and Whiting, forthcoming publication).

The spectrum corresponded exactly with that of the isomerisation product. Final confirmation of structure (XIX) was provided by the ozonolysis of the isomerisation product, the keto-lactone (XV) being obtained.



In addition to studying the action of hydrogen bromide in acetic acid on betulinic acid and its acetate, Robertson *et al.* (*loc. cit.*) also treated the acetate with formic acid, "lactone A" acetate being again obtained. They reported, however, that a different lactone, "lactone B," was obtained by similar treatment both of methyl betulinate and of the free acid. Further investigation of the reactions carried out by Robertson *et al.* have now shown that the two lactones must be identical, since on oxidation with chromic acid they give the same keto-lactone. "Lactone-A" is not easy to purify and is very high melting. It is therefore not suitable for comparison purposes. The corresponding keto-"lactone-A" is easier to purify and characterise.

Experimental.

(All m. p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform.)

The betulin was obtained from birch bark by Ruzicka and Isler's method (*Helv. Chim. Acta*, 1936, **19**, 506).

The oleanolic acid was obtained from spent cloves by the following method.

Partly dried spent cloves (1·5 kg.) were refluxed with ethanol (6 l.) for 2 hours. The warm extract was filtered and concentrated to one-third of its volume, excess of water was added, and the precipitated material filtered off and dried. The crude acid was then suspended in benzene (300 c.c.) and brought into solution by heat. The hot liquid was shaken with sodium hydroxide solution (250 c.c.; 30%). The clear liquor was run off and discarded and the suspension of sodium salt separated from the benzene layer. The suspension was then acidified and the acid collected and dried. The acid (20 g.) obtained after two crystallisations was suspended in hot ethanol, and sodium hydroxide solution was added slowly with shaking until the acid was just in solution. On cooling, the sodium salt which separated in shining needles was collected and washed well with aqueous ethanol. The salt was dissolved in hot ethanol, and the solution acidified with acetic acid, and cooled, whereupon oleanolic acid (12 g.), m. p. 285—300°, separated.

Methyl δ-Oleanonate.—Methyl oleanonate (1 g.) in benzene (10 c.c.) was treated with a mixture of acetic acid (80 c.c.) and sulphuric acid (16 c.c.; d 1·84) with shaking. After 14 days at 20°, dilution with water and isolation with benzene yielded a product (1·09 g.), which was dissolved in benzene (15 c.c.) and chromatographed on a column of alumina (60 g.; activity I). Elution with benzene–ether (6 : 1) (120 c.c.) gave a fraction (880 mg.) which crystallised from chloroform–methanol as needles (460 mg.), m. p. 168—170°. Two further recrystallisations from the same solvent gave *methyl δ-oleanonate*, m. p. 172—173°, $[\alpha]_D^{20}$ −46° (*c*, 1·20), −44° (*c*, 0·76) (Found: C, 79·25; H, 10·3. $C_{31}H_{48}O_3$ requires C, 79·4; H, 10·3%). Light absorption in chloroform–methanol (1 : 1): Max. 2850—2940 Å; $\varepsilon = 36$. Further elution with benzene–ether (5 : 1) (80 c.c.) gave a fraction (150 mg.), crystallisation of which gave oleanonic lactone, m. p. 354—356°, $[\alpha]_D^{20}$ +37° (*c*, 1·11).

Homo-oleanonyl Acetate.—Acetyloleanoloyl chloride (5 g.) in benzene (100 c.c.) was added slowly to methylmagnesium iodide prepared from magnesium (4 g.) and methyl iodide (16 g.) in ether (60 c.c.). After 10 minutes, the temperature was raised and the ether displaced. The benzene solution was then refluxed for 1½ hours. The neutral fraction (3·3 g.) obtained on working up the solution was dissolved in benzene (30 c.c.) and chromatographed on a column of alumina (80 g.; activity I—II). The fraction eluted by benzene–ether (1 : 1) was acetylated in pyridine with acetic anhydride. The acetylated product (3·3 g.) was dissolved in *n*-pentane (40 c.c.), adsorbed on a column of alumina (70 g.; activity I—II), and eluted with *n*-pentane–benzene (4 : 1) (100 c.c., 390 c.c., and 290 c.c.) and benzene (250 c.c.). Fractions of 1·53 g. (m. p. 184—191°), 0·75 g., 0·144 g. (m. p. 208—215°), and 0·72 g. (m. p. 214—217°) were obtained. Crystallisation of fractions 3 and 4 from chloroform–methanol gave flat needles (770 mg.), m. p. 214—217°. Further recrystallisation gave *homo-oleanonyl acetate*, m. p. 215—217°, $[\alpha]_D^{20}$ +66° (*c*, 0·80) (Found: C, 80·05; H, 10·7. $C_{33}H_{54}O_3$ requires C, 79·85; H, 10·55%). Light absorption in chloroform: Max., 2810—2890 Å; $\varepsilon = 62$.

Homo-oleanenedione.—Homo-oleanonyl acetate (700 mg.) was refluxed with alcoholic potassium hydroxide (30 c.c.; 2%) for 1 hour. The crude homo-oleanonol, isolated by dilution with water and extraction with ether, was dissolved in acetone (70 c.c.), and a solution of chromic acid (200 mg.) in water (5 c.c.) and sulphuric acid (0·2 c.c.) added slowly with shaking during 15 minutes. Dilution with water and isolation with ether yielded a product which was chromatographed in benzene–pentane (30 c.c.; 1 : 1) on alumina (40 g.; activity I—II). Elution with benzene (200 c.c.) gave a fraction (380 mg.), two crystallisations of which from methanol gave *homo-oleanenedione*, m. p. 216—222°, $[\alpha]_D^{20}$ +90·5° (*c*, 0·72) (Found: C, 82·05; H, 10·5. $C_{31}H_{44}O_3$ requires C, 82·25; H, 10·7%). Light absorption in chloroform: Max., 2880—2920 Å; $\varepsilon = 123$.

δ-Homo-oleanenedione.—Homo-oleanenedione (250 mg.) was dissolved in benzene (2·5 c.c.), and a

mixture of acetic acid (20 c.c.) and sulphuric acid (4 c.c.; *d* 1·84) added with shaking. After 13 days at 20° dilition with water and isolation with benzene and ether yielded a product which was adsorbed from benzene–pentane (20 c.c.; 1 : 1) on a column of alumina (30 g.; activity I—II). Elution with benzene (120 c.c.) gave a fraction (88 mg.) crystallising from methanol as needles, m. p. 188—198°. Two further recrystallisations from chloroform–methanol gave *δ-homo-oleanenedione*, m. p. 195—198·5°, $[\alpha]_D^{20}$ +22·5° (*c*, 0·40) (Found: C, 82·2; H, 10·9%). Light absorption in ethanol: Inflexion, 2840—2920 Å; ε = 105.

Homolupenonyl Acetate.—Acetylbetulinic acid (7 g.) was dissolved in chloroform (40 c.c.), and thionyl chloride (20 c.c.) was added. After being kept at 20° overnight the solution was added to excess of ether and washed repeatedly with dilute sodium hydroxide (*ca.* 5%) and then with water. The residue (6·6 g.), obtained after drying and evaporation of the ethereal solution, was dissolved in benzene (100 c.c.) and added slowly to methylmagnesium iodide prepared from magnesium (4 g.) and methyl iodide (16 g.) in ether (60 c.c.). After 10 minutes at 20° the temperature was raised and the ether displaced; the benzene solution was then refluxed for 2 hours. The neutral fraction (4·42 g.) obtained on working up the solution was adsorbed from benzene (30 c.c.) on a column of alumina (50 g.; activity I—II). Elution with benzene–ether (1 : 1; 270 c.c.) gave a fraction (2·41 g.) which was acetylated in pyridine with acetic anhydride. The acetylated product (2·94 g.) was dissolved in *n*-pentane (40 c.c.), adsorbed on neutral alumina (60 g.; activity I—II), and eluted with *n*-pentane (100 c.c.) and then *n*-pentane–benzene (1 : 1) (3 × 100 c.c.).

Crystallisation of the first *n*-pentane–benzene (1 : 1) fraction (1·00 g.), m. p. 222—230·5°, from chloroform–methanol gave flakes (507 mg.), m. p. 222—230·5°. Three recrystallisations from the same solvent gave *homolupenonyl acetate*, m. p. 235·5—238°, $[\alpha]_D^{20}$ +24° (*c*, 1·27) (Found: C, 79·9; H, 10·3. $C_{33}H_{52}O_3$ requires C, 79·85; H, 10·55%). Light absorption in alcohol–chloroform: Max., 2920—2950 Å; ε = 44.

Homolupenedione.—Homolupenonyl acetate (389 mg.) in benzene (5 c.c.) was boiled under reflux with alcoholic potassium hydroxide (20 c.c.; 2%) for 1 hour. After the addition of excess of water the product was isolated by extraction with benzene–ether (1 : 1). The crude homolupenonol (341 mg.) was dissolved in chloroform (15 c.c.), and a solution of chromic acid (150 mg.) in acetic acid (10 c.c.)–acetone (20 c.c.)–water (2 c.c.) was added slowly with shaking. After 30 minutes at 20°, dilution with water and isolation with ether yielded a product which was adsorbed from benzene (30 c.c.) on a column of alumina (30 g.; activity I—II). Elution with benzene (200 c.c.) gave a fraction (239 mg.) which crystallised from chloroform–methanol as shining needles (146 mg.), m. p. 191—193·5°. Recrystallisation from chloroform–methanol gave *homolupenedione*, m. p. 193—195°, $[\alpha]_D^{20}$ +48° (*c*, 1·30) (Found: C, 82·15; H, 10·35. $C_{31}H_{48}O_2$ requires C, 82·25; H, 10·7%). Light absorption in ethanol–chloroform; Max. 2910—2930 Å, ε = 63. A further quantity of the diketone (50 mg.) was obtained by oxidation of the fraction (102 mg.) eluted by ethanol–ether (100 c.c.).

Homolupenediol.—To a boiling solution (50 c.c.) of methyl-lithium prepared from lithium (3·4 g.), methyl iodide (42 g.), ether (50 c.c.), and benzene (150 c.c.), acetylbetulinaldehyde (1·0 g.) in benzene (50 c.c.) was slowly added. After refluxing for 16 hours, the cooled solution was poured into dilute hydrochloric acid, and the product isolated by ether-extraction. Treatment of the residue, which had separated during the reaction, with dilute hydrochloric acid and ether gave a further quantity of product. The product (1·33 g.) was adsorbed from benzene (30 c.c.) on a column of alumina (50 g.; activity I). Elution with ether–ethanol (160 c.c.) gave a fraction (1·1 g.) two crystallisations of which from ethanol gave *homolupenediol* as prisms (430 mg.), m. p. 252—262° (decomp.), $[\alpha]_D^{20}$ +15° (*c*, 1·36) (Found: C, 81·45; H, 11·65. $C_{31}H_{52}O_2$ requires C, 81·5; H, 11·45%). Acetylation with acetic anhydride–pyridine gave *homolupenediol diacetate* as needles, m. p. 235—237·5°, $[\alpha]_D^{20}$ +36° (*c*, 0·57) (Found: C, 77·8; H, 10·4. $C_{35}H_{56}O_4$ requires C, 77·75; H, 10·4%).

Oxidation of Homolupenediol.—A solution of homolupenediol (420 mg.) in benzene (10 c.c.) (prepared by warming) was treated with acetone (30 c.c.) and cooled to 20°. Chromic acid (400 mg.) in dilute sulphuric acid (2 c.c.) was added. The precipitate which formed was dissolved by the addition of chloroform (15 c.c.). Chromic acid (200 mg.) and acetone (10 c.c.) were then added. After 30 minutes at 20°, dilution with water and isolation with ether yielded a product (390 mg.) which was adsorbed from benzene (20 c.c.) on a column of alumina (30 g.; activity I). Elution with benzene (3 × 130 c.c.), benzene–ether (1 : 1) (100 c.c.), and ether–ethanol (100 c.c.) gave five fractions: (i) 40 mg., (ii) 100 mg., m. p. 189—194°, (iii) 30 mg., m. p. 191—194°, (iv) 107 mg., m. p. 192—194° and (v) 35 mg. Fractions (ii), (iii), and (iv) were crystallised separately from chloroform–methanol. Fraction (ii): light absorption in chloroform: Max., 2930—2970 Å, ε = 63; $[\alpha]_D^{20}$ +48·5° (*c*, 1·34). Fraction (iv): light absorption in chloroform: Max., 2920—2980 Å, ε = 70·5; $[\alpha]_D^{20}$ +44·5° (*c*, 1·16). A mixed m. p. of fraction (ii) with fraction (iv) or with homolupenedione prepared from homolupenonyl acetate gave no depression.

Isomerisation of Homolupenedione.—Homolupenedione (300 mg.) was dissolved in benzene (3 c.c.), and a mixture of acetic acid (24 c.c.) and sulphuric acid (4·8 c.c.; *d* 1·84) was added with shaking. After 2½ days at 20° one-third of the solution was worked up. The product (110 mg.) was dissolved in benzene (5 c.c.) and adsorbed on a column of alumina (6 g.; activity I). Elution with benzene–ether (1 : 1; 25 c.c.) gave a fraction (65 mg.) which crystallised from methanol as needles, m. p. 220—228°, $[\alpha]_D^{20}$ +66° (*c*, 0·51). Two further recrystallisations gave crystals which melted at 228—235°, followed, at 236°, by the growth of crystals melting at 280° (decomp.). After 14 days the remainder of the solution was worked up. The product (200 mg.) was adsorbed on alumina (6 g.; activity I—II), and the fraction (165 mg.) eluted with benzene–ether (1 : 1; 50 c.c.) crystallised from methanol as needles, m. p. 220—224°, with needles growing at 230° and remelting at 265—275° (decomp.), $[\alpha]_D^{20}$ +61° (*c*, 0·73). A further recrystallisation gave material of m. p. 229—236°. There was no depression

of the m. p. on admixture with the crystals obtained after 2½ days (Found: C, 82·75; H, 10·85. $C_{31}H_{48}O_3$ requires C, 82·25; H, 10·7%). Light absorption in ethanol–chloroform: Max., 2840—2910 Å; $\varepsilon = 38$. Light absorption in ethanol: 2110 ($\varepsilon = 7600$), 2160 ($\varepsilon = 6900$), 2200 ($\varepsilon = 5280$), and 2230 Å ($\varepsilon = 3040$). The crystals gave a yellow colour with tetranitromethane in chloroform.

Ozonolysis of the Product from the Isomerisation of Homolupenedione.—The isomerisation product (103 mg.) was dissolved in chloroform (10 c.c.), and a stream of ozonised oxygen (16 mols.) passed through the solution at 20° for 15 minutes. The solution was evaporated to dryness, and methanol (about 10 c.c.) added. The crystalline residue obtained after evaporation of the methanol was dissolved in benzene (10 c.c.) and adsorbed on to a column of alumina (10 g.; activity I—II). Elution with benzene–ether (2 : 1) (2 × 25 c.c.), after initial elution with benzene (25 c.c.) and benzene–ether (2 : 1) (25 c.c.), gave two fractions: 35 mg., m. p. 312—316°, and 18 mg., m. p. 305—308°. The former fraction was recrystallised three times from chloroform–methanol, to give betulonic lactone as needles, m. p. 334—336°, undepressed with an authentic specimen (see below), $[\alpha]_D^{20}$ +92° (*c*, 0·17).

Action of Sulphuric Acid–Acetic Acid on Methyl Betulonate.—Methyl betulonate (1 g.) was dissolved in benzene (10 c.c.) and a mixture of acetic acid (80 c.c.) and sulphuric acid (16 g.; *d* 1·84) was added with shaking. After 15 days at 20°, dilution with water and isolation with benzene yielded a product which was dissolved in benzene (40 c.c.) and adsorbed on a column of neutral alumina (60 g.; activity I). Elution with benzene (110 c.c.; 80 c.c.) and benzene–ether (6 : 1) (2 × 70 c.c.) gave four fractions: (i) 20 mg., (ii) 120 mg., m. p. 315—320°, (iii) 620 mg., m. p. 318—328° (decomp.), and (iv) 150 mg., m. p. 318—320° (decomp.). Fractions (ii), (iii), and (iv) were crystallised from chloroform–methanol. The combined crystallised fractions (402 mg.) were recrystallised from chloroform–methanol, giving *betulonic lactone* as flat needles, m. p. 333—335°, $[\alpha]_D^{20}$ +88° (*c*, 1·11), +82° (*c*, 2·23) (Found: C, 79·45; H, 10·5. $C_{30}H_{44}O_3$ requires C, 79·25; H, 10·2%).

Action of Formic Acid on Acetylbetulinic Acid.—Acetylbetulinic acid (900 mg.) was boiled under reflux with formic acid (50 c.c.; *d* 1·20) for 5 hours. The mixture was diluted with water, and the product isolated by benzene-extraction. Washing with alkali left a neutral fraction (400 mg.), which was adsorbed from benzene on a column of alumina (40 g.; activity I—II). Elution with ether (120 c.c.) gave a fraction (84 mg.) which crystallised from chloroform–methanol as flat needles, melting above 350°, $[\alpha]_D^{20}$ +57° (*c*, 0·67). This fraction (80 mg.) was dissolved in benzene (10 c.c.), and the solution was boiled under reflux for 1 hour with ethanol (10 c.c.) and potassium hydroxide (1 g.). The product, isolated by ether-extraction, was dissolved in chloroform (5 c.c.) at 30° and a solution of chromic acid (500 mg.) in acetic acid (20 c.c.) was added. After 20 minutes, the product was isolated by dilution with water and extraction with benzene. The product (74 mg.) was dissolved in benzene and adsorbed on a column of alumina (6 g.; activity I—II). Elution with benzene–ether (25 c.c.; 1 : 1) gave a fraction (30 mg.), crystallisation of which from chloroform–methanol gave betulonic lactone as short needles, m. p. 336—337° undepressed when admixed with a specimen prepared from methyl betulonate, $[\alpha]_D^{20}$ +82° (*c*, 0·56).

Action of Formic Acid on Betulinic Acid.—Betulinic acid (2·4 g.) was boiled under reflux with formic acid (70 c.c.; *d* 1·2) for 4 hours. The mixture was diluted with water, and the product was isolated by benzene-extraction. The neutral fraction (420 mg.) was boiled under reflux with benzene (20 c.c.), ethanol (20 c.c.), and potassium hydroxide (5 g.) for 30 minutes. The product (350 mg.), isolated by dilution with water and extraction with ether, was dissolved in chloroform (25 c.c.), chromic acid (2·5 g.) in acetic acid (100 c.c.) was added slowly, with shaking, and the mixture kept at 20° for 30 minutes. The product, isolated by benzene-extraction, was dissolved in benzene and adsorbed on a column of alumina (30 g.; activity I—II). Elution with benzene–ether (80 c.c.; 1 : 1) gave a fraction (110 mg.) which was crystallised from chloroform–methanol, to give flat needles, m. p. 327—328·5°. Two recrystallisations from the same solvent gave betulonic acid lactone, m. p. 337—338° undepressed when admixed with a specimen prepared from methyl betulonate, $[\alpha]_D^{20}$ +78° (*c*, 0·75).

Reductive Fission of Betulonic Lactone by Lithium Aluminium Hydride.—Betulonic lactone (1 g.) was dissolved in tetrahydrofuran (100 c.c.) under reflux and freshly powdered lithium aluminium hydride (500 mg.) added to the cooled solution. After the initial reaction the mixture was refluxed for 30 minutes. Excess of lithium aluminium hydride was then decomposed by careful addition of water. After the addition of excess of dilute hydrochloric acid the product (1·14 g.) was isolated with ether and crystallised from acetone–chloroform–methanol, to give flat needles (824 mg.), m. p. 247—255°. Three further recrystallisations from methanol gave the triol as flat needles, m. p. 259—267°. Further purification was effected by hydrolysis of the triol diacetate (see below). The diacetate (50 mg.) was boiled under reflux with alcoholic potassium hydroxide (10 c.c.; 2%) for 1 hour. Dilution with water and extraction with ether gave the *triol* which crystallised from methanol as needles, m. p. 296—298°, $[\alpha]_D^{20}$ +24° (*c*, 0·69) (Found: C, 77·8; H, 11·45. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·4%).

Acetylation of the Triol.—(a) *Use of acetic anhydride–pyridine at* 100°. The triol (756 mg.) was heated on the steam-bath with acetic anhydride (40 c.c.) and pyridine (20 c.c.) for 2½ hours. The warm solution was then poured into excess of water, and the product (1·0 g.), isolated with benzene, was chromatographed in benzene–pentane (30 c.c.; 1 : 1) on alumina (40 g.; activity I—II). After elution with benzene–*n*-pentane (1 : 1) (520 c.c.), and benzene (280 c.c.), elution with benzene (640 c.c.) and benzene–ether (1 : 1) (140 c.c.) gave a series of fractions melting at *ca.* 240° after crystallisation from methanol. The combined crystallised fractions (500 mg.) were recrystallised from chloroform–methanol, giving the *triol diacetate* as short needles, m. p. 240—242·5°, $[\alpha]_D^{20}$ +22° (*c*, 0·78) (Found: C, 74·65; H, 10·75. $C_{34}H_{56}O_5$ requires C, 74·95; H, 10·4%).

(b) *Use of boiling acetic anhydride–pyridine.* The triol (104 mg.) was refluxed with acetic anhydride (25 c.c.) and pyridine (5 c.c.) for 100 minutes. Dilution of the slightly cooled solution with water and isolation with benzene yielded a product (121 mg.) which was chromatographed in pentane (20 c.c.) on

alumina (10 g.; activity I—II). After elution with *n*-pentane and *n*-pentane–benzene, elution with benzene (75 c.c.) gave a fraction (61 mg.), m. p. 213—214°. After further elution with benzene (25 c.c.), a fraction (27 mg.), m. p. 242—244°, was obtained with benzene–ether (1 : 1) (25 c.c.). Crystallisation of the fraction melting at 213—214° from methanol gave the triol triacetate as prisms, m. p. 213—214°, undepressed on admixture with a specimen of the triacetate prepared by method (c). Crystallisation of the fraction melting at 242—244° from methanol gave the triol diacetate, m. p. 242—244° undepressed on admixture with a specimen prepared by method (a).

(c) *Use of boron trifluoride catalyst.* The triol (497 mg.) was suspended in acetic anhydride (120 c.c.) and boron trifluoride–acetic acid complex (4 c.c.) added dropwise with shaking. After 18 hours at 20°, dilution with water and isolation with benzene–ether (1 : 1) yielded a gum (766 mg.) which was adsorbed from benzene–*n*-pentane (30 c.c.; 1 : 2) on a column of alumina (50 g.; activity I–II). After elution with *n*-pentane–benzene (2 : 1) (100 c.c.), elution with *n*-pentane–benzene (1 : 1) (200 c.c.; 100 c.c.) and benzene (150 c.c.; 100 c.c.) gave fractions: (i) 130 mg., m. p. 277—277·5°, (ii) trace, (iii) 220 mg., m. p. 212—214·5°, and (iv) 29 mg. Crystallisation of fraction (i) from chloroform–methanol gave flakes, m. p. 277—277·5° (50 mg.). Recrystallisation from the same solvent gave moradiol diacetate, m. p. 278—278·5°, $[\alpha]_D^{20}$ +27° (*c*, 0·44) (Found: C, 77·6; H, 10·25. Calc. for $C_{34}H_{54}O_4$: C, 77·5; H, 10·3%). A mixed m. p. with an authentic specimen of moradiol diacetate, m. p. 277·5—278°, $[\alpha]_D^{20}$ +22° (*c*, 1·75), gave no depression. Crystallisation of fraction (iii) from methanol gave prisms, m. p. 212—214·5°. Further recrystallisations from methanol gave the *triol triacetate*, m. p. 213—216° (Found: C, 74·0; H, 9·55. $C_{36}H_{56}O_6$ requires C, 73·7; H, 9·95%).

Hydrolysis of Moradiol Diacetate using Lithium Aluminium Hydride.—Moradiol diacetate (26 mg.) was dissolved in benzene (5 c.c.) and a solution of lithium aluminium hydride in ether (5 c.c.; approx. 0·9%) was added. After five minutes' refluxing, water was cautiously added dropwise, followed by excess of dilute sulphuric acid. Extraction with ether gave a product which crystallised from chloroform–methanol as flat needles (14 mg.), m. p. 201—209°. Two recrystallisations from methanol gave moradiol as flat needles, m. p. 221—223° undepressed when admixed with an authentic specimen, $[\alpha]_D^{20}$ −17° (*c*, 0·47). The authentic specimen had m. p. 221—223·5°, $[\alpha]_D^{20}$ −9° (*c*, 0·5).

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600. *The Chemistry of the Triterpenes. Part X.* The Structures of Some Isomerisation Products from Betulin and Betulinic Acid.*

By G. S. DAVY, T. G. HALSALL, E. R. H. JONES, and G. D. MEAKINS.

The structures suggested in the preceding paper for the keto-lactone obtained from betulinic acid, and for its lithium aluminium hydride reduction product have been confirmed. A relationship between the lactone and *allo*-betulin has been established and the structure of *allo*betulin is now formulated for the first time.

The stereochemistry of rings D and E of the keto-lactone and the triol derived from it has been elucidated.

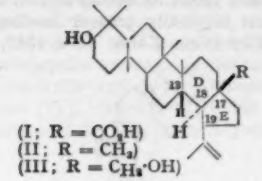
A preliminary account of part of this work has already been published (Davy, Halsall, and Jones, *Chem. and Ind.*, 1951, 233).

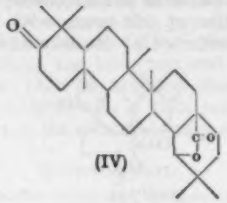
IN Part IX of this series,* the conversion of betulinic acid (I) into a keto-lactone (IV) has been described. The lactone was reduced with lithium aluminium hydride to a triol (V) which, on vigorous acetylation, underwent dehydration giving the diacetate of moradiol (VI). Structure (V) for the triol followed from the known structure (VI) (Barton and Brooks, *J.*, 1951, 257) provided that no rearrangement of the carbon skeleton accompanied or followed dehydration, a possibility which, however, could not immediately be excluded in view of the employment of powerful acidic catalyts (boron trifluoride and perchloric acid).

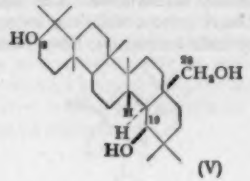
In order to confirm structure (V) a study of the properties of the triol diacetate, formed by acetylation with acetic anhydride–pyridine, was begun. On dehydration of this diacetate with phosphorus oxychloride in pyridine at 100° moradiol diacetate was again formed. The two easily acetylated hydroxyl groups of the triol must be those located at $C_{(3)}$ and $C_{(28)}$, the readily eliminated hydroxyl group not being acetylated. This lack of reactivity suggests that

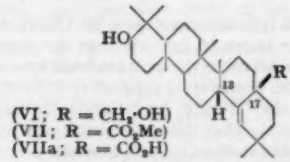
* Part IX, preceding paper.

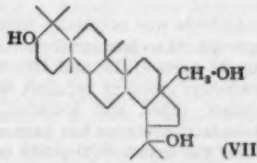
this hydroxyl group is either tertiary, or secondary but sterically hindered. A tertiary hydroxyl group could be accommodated by formulating the triol as (VIII), but this is excluded





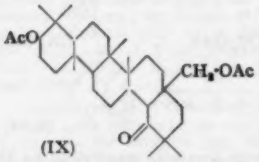


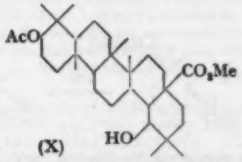


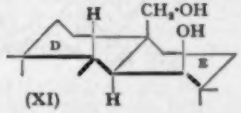


since the triol diacetate can be oxidised by chromic acid to the keto-diacetate (IX) which, in turn, can be reduced back to the parent triol by lithium aluminium hydride as described below.

Dehydration of the triol diacetate may be carried out with both boron trifluoride–acetic anhydride at 20° (rather than at 100°) *and* the milder reagent, phosphorus oxychloride in pyridine at 100°, moradiol diacetate again being produced in both cases. The smooth dehydration under the latter conditions tends to discount the possibility of rearrangement following dehydration. An analogous elimination of a $C_{(19)}$ hydroxyl group with phosphorus oxychloride in pyridine has been described by Barton, Brooks, and Holness (*J.*, 1951, 278), who report the conversion of methyl dihydrosiaresinolate acetate (X) into the acetate of methyl morolate (VII). The structure of the triol (V) has been confirmed still further by the preparation of both its diacetate and the keto-diacetate (IX) by the alternative route discussed below.





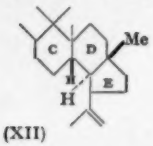


The ease of dehydration, the resistance to acetylation, and the relative ease of oxidation of the hydroxyl group at $C_{(19)}$ indicate that it is polar (Barton, *Experientia*, 1950, **6**, 316). Further, the ease and method of dehydration indicate that the hydroxyl group at $C_{(19)}$ and the hydrogen atom at $C_{(18)}$ eliminated with it are *trans* to one another. The formation of the triol by lithium aluminium hydride scission of the lactone ring of (IV) leads to the conclusion that in the triol the primary alcohol group at $C_{(17)}$ must be *cis* to the hydroxyl group at $C_{(19)}$, *i.e.*, also polar. Hence, the primary alcohol group is *trans* to the hydrogen atom at $C_{(18)}$, *i.e.*, rings D and E in the triol (V) [cf. (XI)], and hence in the lactone (IV), are *trans*-fused.

Provided that the formation of the keto-lactone (IV) from betulinic acid (I) does not involve the D–E ring fusion, it may be concluded that in this acid, and hence in the lupeol group of triterpenes [lupeol (II); betulin (III)], rings D and E are *trans*-fused, with the substituent at $C_{(17)}$ polar, in contrast to the *cis*-linking of rings D and E in the β-amyrin series (see below). On the basis of present knowledge this conclusion is believed to be correct, but further evidence is being sought in order to establish it rigorously.

Barton and Brooks (*loc. cit.*) have shown that in moradiol (VI) the primary alcohol group at $C_{(17)}$ is *cis* relative to the hydrogen atom at $C_{(18)}$. A similar relation must hold in the triol (V), and consequently in the lupeol group of triterpenes the substituent at $C_{(17)}$ is *cis* to the hydrogen atom at $C_{(18)}$. The stereochemistry of rings D and E of the lupeol group can therefore be represented provisionally by (XII), that of rings A and B being already known

(cf. Barton, *loc. cit.*; Gutmann, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 1154). The configuration of the *iso*propenyl group is not indicated as it is not yet regarded as being definitely established. The degradation of the *iso*propenyl side chain of betulinic acid to a carboxyl group, and the interaction of this group with that originally present leading to anhydride formation, have been described by Ruzicka and Rey (*Helv. Chim. Acta*, 1943, **25**,



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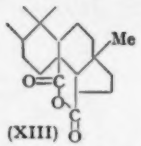
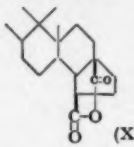


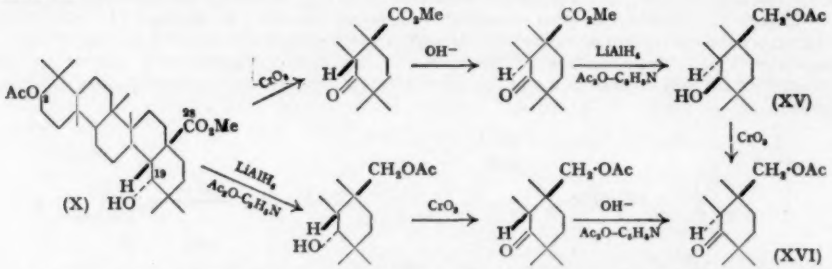
(XIII)



(XIV)

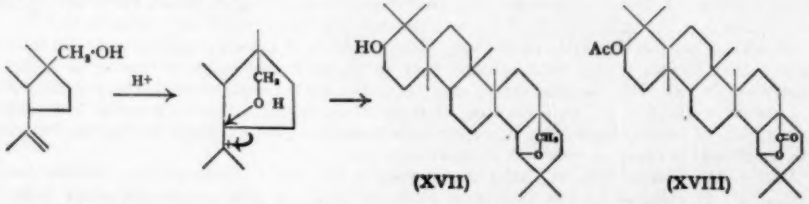
2143). The anhydride was originally formulated as (XIII) but must now be (XIV) with the two carboxyl groups *cis* to one another. This might be taken to indicate that the *iso*propenyl group of the lupeol series (I, II, and III) must be *cis* relative to the polar substituent at $C_{(17)}$, *e.g.*, the $C_{(17)}$ carboxyl group of betulinic acid. There is, however, a possibility of inversion at $C_{(19)}$ (cf. Gutmann, Jeger, and Ruzicka, *loc. cit.*) either during degradation or anhydride formation and, in fact, evidence has been obtained recently that this possibility may represent the truth and that the *iso*propenyl group is probably *trans* to the $C_{(17)}$ substituent.

While the work described above was in progress Dr. Barton kindly disclosed to us his results concerning the *cis*-fusion of rings D and E of the β-amyrin group and, in particular, of siaresinolic acid (Barton and Holness, *Chem. and Ind.*, 1951, 233). On consideration of these results it became clear that still further confirmation of the structure (V) deduced above for the triol could be obtained since its 2 : 28-diacetate and the 19-keto-derivative of this diacetate (IX) should be produced from methyl dihydrosiaresinolate acetate (X) by the following series of reactions.



Compounds (XV) and (XVI) prepared by Barton and Holness (*loc. cit.*) according to the above scheme have fulfilled this prediction, proving to be identical with the triol 2 : 28-diacetate and (IX), as shown by their identical constants and by mixed melting-point determinations.

The elucidation of the nature of the lactones formed when betulinic acid and its derivatives are treated with strong acids suggested that the production of the saturated ether, *allo*betulin, by formic acid isomerisation of betulin (Schulze and Pieroh, *Ber.*, 1922, **55**, 2332) might take place in an analogous manner :



This leads to structure (XVII) for *allo*betulin. The oxidation of *allo*betulin acetate with nitric acid (Dischendorfer and Polak, *Monatsh.*, 1929, **51**, 43) or chromic acid (Schulze and Pieroh, *loc. cit.*) gives the so-called oxy*allo*betulin acetate (m. p. >335°; $[\alpha]_D$ +60° in chloroform), in

which two hydrogen atoms have been replaced by an oxygen atom. Dr. Barton drew our attention to this compound and suggested that it might be identical with the acetoxy-lactone (XVIII) (m. p. >350°; $[\alpha]_D$ +57° in chloroform) obtained from betulinic acid acetate. As pointed out by Davy, Halsall, and Jones (preceding paper) the most suitable compound for comparison is the lower-melting keto-lactone (IV). The corresponding derivative from oxy*allo*betulin acetate, oxy*allo*betulone, has been prepared by a method similar to that of Dischendorfer and Juvan (*Monatsh.*, 1930, **56**, 242) and shown to be identical with the keto-lactone (IV). Structure (XVII) for *allo*betulin is thus confirmed, oxy*allo*betulin arising by oxidation of the CH_2 group adjacent to the ethereal oxygen atom of *allo*betulin.

Experimental.

All m. p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform. Light petroleum refers to the fraction with b. p. 40—60° unless otherwise stated. The alumina used for chromatography had an activity of I—II.

Treatment of the Triol Diacetate with Boron Trifluoride–Acetic Anhydride.—The triol diacetate (100 mg.) was dissolved in acetic anhydride (30 c.c.), and boron trifluoride–acetic acid complex (0·5 c.c.) was added dropwise with shaking. After 18 hours at 20°, the solution was added to excess of water. The product (127 mg.), isolated by extraction with benzene–ether (1 : 1), was adsorbed from light petroleum–benzene (30 c.c.; 2 : 1) on a column of alumina (13 g.). Elution with light petroleum–benzene (1 : 1; 25 c.c.) gave a crystalline fraction (27 mg.) which was crystallised from chloroform–methanol, yielding moradiol diacetate, m. p. 274·5—276° undepressed with an authentic specimen (m. p. 277—278°). Elution with benzene (50 c.c.) gave a gum (61 mg.) which could not be crystallised but was probably the triol triacetate.

Action of Phosphorus Oxychloride in Pyridine on the Triol Diacetate.—The triol diacetate (100 mg.) was dissolved in dry pyridine (15 c.c.) and phosphorus oxychloride (3 c.c.) added. The solution was heated at 100° for 1½ hours, then cooled, and cautiously added to excess of water. The product (90 mg.), isolated by ether-extraction, was adsorbed from *n*-pentane–benzene (10 c.c.; 1 : 1) on a column of alumina (10 g.). The following fractions were eluted with *n*-pentane–benzene (1 : 1) (4 × 25 c.c.): (i) trace, (ii) 24 mg., m. p. 276·5°, (iii) 40 mg., m. p. 269·5—274°, and (iv) 4 mg. A further fraction (v), 42 mg., m. p. 240—244°, was eluted with ether (50 c.c.). Crystallisation of (ii) and (iii) from chloroform–methanol gave moradiol diacetate, m. p. 276·5—277·5°, undepressed with an authentic specimen (m. p. 277—278°). Crystallisation of fraction (v) from chloroform–methanol gave unchanged triol diacetate.

Oxidation of the Triol Diacetate.—The triol diacetate (477 mg.) was dissolved in chloroform (22 c.c.), and a solution of chromic acid (220 mg.) in acetic acid (15 c.c.), acetone (30 c.c.), and water (2·5 c.c.) was added slowly with shaking. After 45 minutes at 20°, the mixture was diluted with water, and the product isolated by extraction with benzene–ether (1 : 1). Crystallisation of the product from methanol afforded undefined crystals, m. p. 221—340° (decomp.). Concentration of the mother-liquors gave material (80 mg.) as flakes, m. p. 215—220°. Recrystallisation of these from methanol gave the *keto-diol diacetate* (IX), m. p. 220—222·5° undepressed on admixture with the sample of m. p. 222—224°, $[\alpha]_D$ +41° (*c*, 1·13), prepared by Barton and Holness (*loc. cit.*), $[\alpha]_D^{20}$ +37° (*c*, 0·90) (Found: C, 75·25; H, 10·25. $C_{34}H_{54}O_8$ requires C, 75·25; H, 10·05%). Light absorption in ethanol: Max. 2940—2980 Å; $\varepsilon = 34$.

Oxy*allo*betulone (IV).—To a boiling solution of *allo*betulin acetate (663 mg.) in acetic acid (70 c.c.), chromic acid (823 mg.) in acetic acid (60 c.c.) was slowly added. After boiling under reflux for 15 minutes the mixture was cooled and diluted with water. The product (493 mg.) obtained by chloroform-extraction was adsorbed from light petroleum–benzene (1 : 1) (150 c.c.) on a column of alumina (50 g.). The fractions eluted with benzene (400 c.c.) and benzene–ether (1 : 1) (750 c.c.) were combined and crystallised from chloroform–methanol, to give oxy*allo*betulin acetate as plates (350 mg.), m. p. >360°.

The acetate (220 mg.) was dissolved in benzene (120 c.c.) and boiled under reflux for 2 hours with a solution of potassium hydroxide (5 g.) in 95% ethanol (100 c.c.). The reaction mixture was diluted with water, and the product (156 mg.), isolated by chloroform-extraction, was dissolved in chloroform (20 c.c.) and added to a solution of chromic acid (100 mg.) in acetic acid (100 c.c.). After 18 hours at 20° the mixture was diluted with water. The neutral product, isolated by chloroform extraction, was adsorbed from benzene on a column of alumina (10 g.). The fraction (70 mg.) eluted with benzene was crystallised several times from chloroform–methanol, giving oxy*allo*betulone as rods (45 mg.), m. p. 333—334° undepressed on mixing with a specimen of the keto-lactone A from betulonic acid, $[\alpha]_D^{20}$ +84·7° (*c*, 1·05) (Found: C, 79·0; H, 9·8. Calc. for $C_{30}H_{44}O_3$: C, 79·2; H, 10·2%). During the melting-point determination a change of crystal form (rods ⟶ needles) occurs at *ca.* 230°. Dischendorfer and Juvan (*loc. cit.*) report a rotation of $[\alpha]_D$ −6° in benzene for oxy*allo*betulone.

Thanks are offered to Mr. E. S. Morton and Mr. H. Swift for microanalyses and to Miss E. Fuller for the ultra-violet absorption spectra. One of the authors (G. S. D.) thanks the University of Manchester for a post-graduate scholarship.

The University, Manchester, 13. [*Received, July 5th*, 1951.]

601. *Aryl-2-halogenoalkylamines. Part IX.* A Comparison of the Stability of Esters derived from Some Aryl-2-halogenoalkylamines towards Acid Hydrolysis with Those obtained from Other Radiomimetic Compounds.*

By W. Davis and W. C. J. Ross.

The rates of hydrolysis of acetates derived from some aryl-2-halogenoalkylamines under acid conditions and in 80% aqueous acetone have been measured and compared with those of esters derived from sulphur and nitrogen " mustards " and also from ethylene oxide. Under these conditions the stability of the various esters is comparable with that of ethyl and *iso*propyl acetates.

In Part VIII • it was shown that acetates and benzoates derived from so-called " radiomimetic " alkylating agents such as sulphur and nitrogen " mustards " and also certain epoxides were more rapidly hydrolysed under alkaline conditions than simple alkyl esters. There was a wide variation in the velocity constants for the hydrolysis of the different esters, those derived from epoxides being by far the most alkali-labile. It was realised that the rates of hydrolysis under these conditions did not necessarily bear any direct relation to the ease of hydrolysis of the various esters under physiological conditions. In order to obtain more complete information regarding the relative stability of esters derived from the various cytotoxic agents the acid hydrolysis of a series of these esters has now been studied. The relative stabilities to acid hydrolysis were of particular interest since it is later hoped to treat proteins with the different alkylating agents and then by degradation of the products by acid to attempt to decide which amino-acid residues had combined with the reagent.

In the present study the acetates derived from the following compounds have been examined : 2-chloroethyldimethylamine, di-2-chlorethylmethylamine, 2-chloroethyl ethyl sulphide, di-2-chloroethyl sulphide (mustard gas), *N*-2-chloroethyl-*N*-ethylaniline, *NN*-di-2-chloroethylaniline, *NN*-di-2-chloroethyl-*p*-anisidine, di-2-chloroethyl-β-naphthylamine, and di-2-chloro-*n*-propyl-β-naphthylamine. Since the rates of hydrolysis of acetates and benzoates under alkaline conditions were previously found to be in the same relative order it was not deemed necessary to examine the benzoates in the present study. The acetates were prepared by the methods described in Part VIII.

Methods.

On account of the very low aqueous solubility of the esters derived from the sulphur and nitrogen " mustards " it was necessary to carry out the determinations of the rates of hydrolysis in 80% acetone. The hydrolyses were made in sealed Pyrex bulbs, essentially by the method of Timm and Hinshelwood (*J.*, 1938, 864). Table I shows the details for the hydrolysis of di-2-acetoxyethyl sulphide. The fact

Table I.

Hydrolysis of di-2-acetoxyethyl sulphide in 80% *aqueous acetone.*

Ester used for each determination, 51·8 mg. 0·025N-Hydrochloric acid used in each run, 20 ml. Total reaction solution, 100 ml. Equivalent vol. (*a*) of 0·025N-acid which would be liberated at complete hydrolysis, 20·1 ml. Temp., 50°. pH of solution, 1·9.

Time (hours).	0·025N-NaOH for titration (ml.).	0·025N-acid liberated (ml.), *x*.	$\log_{10} a/(a - x)$.
0	21·50	—	—
42·5	24·75	3·25	0·077
66·75	26·50	5·00	0·126
90·25	27·95	6·45	0·169
118·5	29·40	7·90	0·217

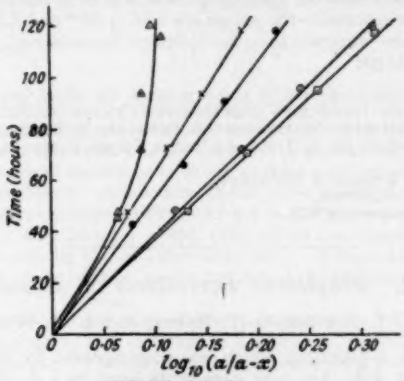
From the figure the slope of the line $2{\cdot}303/k[H^+] = 120 \times 3600/0{\cdot}2225$. Since $[H^+] = 0{\cdot}005$, $k = 2{\cdot}36 \times 10^{-4}$.

that a plot of *t* against $\log a/(a - x)$ (see figure)—the slope of this line is $2{\cdot}303/k[H^+]$—is generally linear over the first 40% of the reaction shows that the re-esterification reaction can be disregarded. Other data are recorded in the figure. The value of the hydrogen-ion concentration used in the calculation of the rate constant *k* was taken as 0·005 equiv. per l., it being assumed that dissociation of the hydrochloric

* Part VIII, *J.*, 1950, 3056.

acid was complete. The pH of a solution containing this concentration of acid in 80% acetone was found to be 1·9 by means of a glass electrode system with a Cambridge portable electrometer valve pH meter—a value of 2·3 would have been obtained in purely aqueous solution. It is well known that anomalous values are obtained when pH measurements are made with glass electrodes in non-aqueous solutions (Dole, "The Glass Electrode," New York, 1941). In the present studies the glass electrode is simply being used to ensure that the hydrogen-ion concentration is the same in all the hydrolyses.

Addition of most of the esters now examined to the 80% acetone solution of hydrochloric acid did not affect the pH reading determined as above and this reading remained constant throughout the reaction. Di-2-acetoxyethylmethylamine, 2-acetoxyethyldimethylamine, and *N*-2-acetoxyethyl-*N*-ethylaniline, which have pK_a values in 80% acetone of 5·7, 7·3 (Davis and Ross, *loc. cit.*), and 2·4 respectively, were sufficiently basic to reduce the hydrogen-ion concentration by salt formation. The pH of these solutions



was adjusted by addition of hydrochloric acid to give a meter reading of 1·9 at the start of the reaction. It is realised that the value of the hydrogen-ion concentration used in the calculations may not be strictly correct but since in all reaction mixtures the meter reading was the same the values of k given in Table II represent the relative stability of the esters towards acid hydrolysis.

The pK_a of the di-2-acetoxyethylarylamines investigated was lower than 0·5 in 80% acetone solution.

Hydrolysis of 2-acetoxyethyldimethylamine gave anomalous results, for although the pH of the reaction solution remained constant throughout the experiment the velocity constant fell steadily from $1·76 \times 10^{-4}$ at 48 hours to $1·04 \times 10^{-4}$ at 120 hours.

Discussion.

The results given in Table II show that generally esters derived from the cytotoxic chloroethylamines and chloroethyl sulphides are somewhat more stable to acid hydrolysis than is ethyl acetate. This contrasts sharply with the greater alkali-lability of the same esters. The slowest rates were observed for di-2-acetoxyethylmethylamine and 2-acetoxyethyldimethylamine, which are sufficiently basic to be present in the cationic form under the chosen reaction conditions; however, the rate constant for *N*-2-acetoxyethyl-*N*-ethylaniline, some 60—70% of which will be present in the cationic form, is not especially low. The rate constants for the aliphatic esters are about one-half of that for ethyl acetate. There is no significant difference

Table II.

Second-order velocity constants for acid hydrolysis at 50° in 80% acetone.

Compound.	10^4k.	Compound.	10^4k.
$CH_3·CH_2·OAc$	3·28	$Ph·N(CH_2·CH_3)·[CH_2]_2·OAc$	2·33
$(CH_3)_2CH·OAc$	1·96	$Ph·N([CH_2]_2·OAc)_2$	2·18
$(CH_3)_2N·[CH_2]_2·OAc$	1·76—1·04	p-$MeO·C_6H_4·N([CH_2]_2·OAc)_2$	2·06
$CH_3·N([CH_2]_2·OAc)_2$	1·54	β-$C_{10}H_7·N([CH_2]_2·OAc)_2$	2·06
$CH_3·CH_2·S·[CH_2]_2·OAc$	2·38	β-$C_{10}H_7·N(CH_2·CHMe·OAc)_2$	1·96
$S([CH_2]_2·OAc)_2$	2·36	$HO·CH_2·CH_2·OAc$	3·46

between the rates of hydrolysis of *iso*propyl acetate and the ester of di-2-hydroxy-*n*-propyl-β-naphthylamine which has a comparable structure.

The variation of the alcohol component of the esters thus has much less effect on the rate of acid hydrolysis that it has on alkaline hydrolysis (cf. Hammett, " Physical Organic Chemistry," New York, 1940, p. 213), in particular, the monoester of ethylene glycol which is hydrolysed approximately ten times as fast as ethyl acetate by alkali is hydrolysed by acid at practically the same rate as the latter. This might have been expected since in acid solution the hydroxy-ester could not assume the ionic form which was regarded as responsible for the high rate of hydrolysis in alkali (Davis and Ross, *loc. cit.*).

A comparison of the second-order velocity constants in 80% acetone for the acid- and base-catalysed hydrolyses now reported—the values are $2{\cdot}36 \times 10^{-4}$ and 8100×10^{-4} respectvely for di-2-acetoxyethyl sulphide—suggests that the hydroxyl-ion-catalysed reaction will be far more significant at physiological pH.

This investigation has been supported by grants made to the Royal Cancer Hospital by the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the Division of Research Grants of the U.S. Public Health Service, and was carried out during the tenure by one of the authors (W. C. J. R.) of a British Empire Cancer Campaign Fellowship.

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602. *Ethylidene Derivatives of Mannitol.*

By E. J. Bourne, G. T. Bruce, and L. F. Wiggins.

Triethylidene D-mannitol, which was first reported by Meunier (*Compt. rend.*, 1889, **108**, 408), has now been hydrolysed to a diethylidene and a monoethylidene mannitol, which are proved conclusively to be, respectively, the 1 : 3-4 : 6- and the 1 : 3-derivative; thus the parent triacetal is 1 : 3-2 : 5-4 : 6-triethylidene D-mannitol.

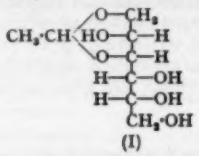
It is now some sixty years since Meunier (*Compt. rend.*, 1889, **108**, 408), and later Delépine (*ibid.*, 1900, **131**, 745), described the preparation of a crystalline triethylidene D-mannitol from D-mannitol and paraldehyde in the presence of a concentrated mineral acid (sulphuric, hydrochloric). In 1948, Bourne and Wiggins (*J.*, 1948, 1933) demonstrated that a crystalline triethylidene hexitol, obtained in small yield from commercial sorbitol and claimed by Appel (*J.*, 1935, 425) to be " triethylidene sorbitol," was in fact identical with Meunier's compound and gave D-mannitol hexa-acetate when hydrolysed and then acetylated. There has been, hitherto, no evidence upon which a structure could be assigned to this triacetal. As a part of our studies on the pattern of condensations between carbonyl compounds and polyhydric alcohols, we have proved that the ethylidene groups span the 1 : 3-, 2 : 5-, and 4 : 6-positions of the mannitol moiety.

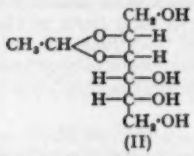
Graded acidic hydrolysis of the triacetal afforded, in addition to unchanged starting material and D-mannitol, two new crystalline compounds, *viz.*, a di- and a mono-ethylidene D-mannitol. Treatment of each of these products with the appropriate reagents gave the original triethylidene D-mannitol, so that there was no doubt that they possessed the D-mannitol configuration.

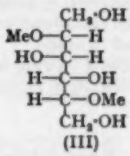
The monoethylidene compound (m. p. 163·5—165°) was not the 3 : 4-ethylidene D-mannitol (m. p. 107—109°) prepared by Wiggins (*J.*, 1946, 384). Moreover, its crystalline tetrabenzoate was different from that produced when the well-characterised 1 : 2 : 5 : 6-tetrabenzoyl D-mannitol was treated with paraldehyde and hydrobromic acid.

The new monoethylidene D-mannitol was characterised almost completely by its behaviour towards glycol-splitting reagents. First, it consumed two molecular proportions of lead tetra-acetate in glacial acetic acid at room temperature, showing that the four free alcohol groups were present, either as two α-glycol groups or as a vicinal triol removed from the fourth hydroxy-group. This observation limited the structure for the acetal to five possibilities, *viz.*, the 1 : 3-, 1 : 4-, 1 : 5-, 2 : 3-, and 3 : 4-compounds; the configuration of mannitol is such that the first four of these are identical with the 4 : 6-, 3 : 6-, 2 : 6-, and 4 : 5-isomers, respectively. Secondly, oxidation with sodium metaperiodate at room temperature afforded one molecular proportion of formic acid and also of formaldehyde, the latter being isolated as its crystalline

dimedone derivative. Such a result was to be expected only from an ethylidene D-mannitol in which the 4 : 5 : 6-positions (the 1 : 2 : 3-positions are identical) were unsubstituted, leaving only the 1 : 3- (I) and the 2 : 3-derivative (II) for further consideration. The deductions thus far made were confirmed by the demonstration that the larger fragment of the oxidative cleavage analysed correctly for an ethylidene tetrose and gave D-erythrosazone on hydrolysis and treatment with phenylhydrazine.


(I)

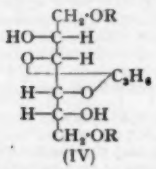

(II)


(III)

An indication that the ethylidene D-mannitol was in fact the 1 : 3-acetal was obtained when it was shown that its tetratoluene-*p*-sulphonate gave only 0·97 molecular proportions of sodium toluene-*p*-sulphonate when it was heated at 100—110° with sodium iodide in dry acetone. The isomeric ester of the 2 : 3-acetal should have given at least two molecular proportions of the sodium salt under these conditions. Since there is still some dubiety concerning the behaviour of vicinal toluene-*p*-sulphonate groups when submitted to the sodium iodide exchange reaction (for a summary see Bladon and Owen, *J.*, 1950, 598), we do not regard this evidence alone as conclusive. However, as will be shown later, only the 1 : 3-structure offered a satisfactory explanation of the conversion of the above-mentioned diethylidene D-mannitol into the monoacetal.

Attention was next turned to the diethylidene D-mannitol, in which the presence of two hydroxy-groups was confirmed by the isolation of a diacetate, a ditoluene-*p*-sulphonate, and a dimethyl ether, all crystalline. The diacetal did not react with lead tetra-acetate, showing that it was devoid of an α-glycol group, and its ditoluene-*p*-sulphonate was recovered unchanged after being heated at 100—105° with sodium iodide in acetone, indicating that the acetal groups probably engaged both of the primary alcohol groupings. Only the 1 : 3 : 5 : 6- and the 1 : 3 : 4 : 6-structure were consistent with this evidence (N.B. the 1 : 2 : 4 : 6-structure is identical with the former).

Hydrolysis of the dimethyl ether of the diethylidene D-mannitol afforded a syrupy dimethyl D-mannitol, which was purified *via* its crystalline tetra-acetate. The dimethyl mannitol was proved, by two independent routes, to carry its substituents at positions 2 and 5. First, the compound consumed one molecular proportion of sodium metaperiodate, without the concomitant liberation of either formaldehyde or formic acid; of all the possible dimethyl D-mannitols only the 2 : 5-derivative (III) should behave in this way. Secondly, the same crystalline tetra-acetyl dimethyl D-mannitol was synthesised by an alternative method, in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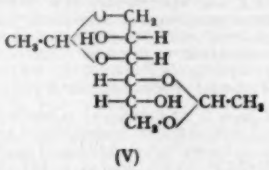
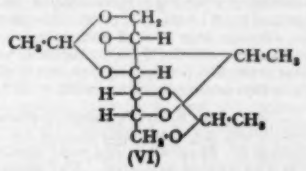

(V)


(VI)

which the parent compound was the well-known 3 : 4-*iso*propylidene D-mannitol (IV; R = H) (for proof of the structure see Müller, *Ber.*, 1932, **65**, 1055; Brigl and Grüner, *Ber.*, 1933, **66**, 931; Fischer and Appel, *Helv. Chim. Acta*, 1934, **17**, 1574). 3 : 4-*iso*Propylidene D-mannitol, when treated with 2 molecular proportions of triphenylmethyl chloride in pyridine (cf. Müller, *loc. cit.*), readily gave a ditrityl ether (IV; R = CPh_3), very probably the 1 : 6-derivative (cf. Helferich, *Adv. Carbohydrate Chem.*, 1948, **3**, 79). Methylation and subsequent hydrolysis then afforded syrupy 2 : 5-dimethyl D-mannitol (III). The behaviour of this towards sodium metaperiodate was identical with that of the dimethyl D-mannitol obtained from diethylidene mannitol, and its acetylation gave the crystalline tetra-acetyl dimethyl D-mannitol already described.

This evidence allows three possible structures for diethylidene D-mannitol, *viz.*, 1 : 3-4 : 6-, 1 : 4-3 : 6-, and 1 : 6-3 : 4-, of which the first is the most reasonable stereochemically. That

this is indeed the correct structure has been shown by careful hydrolysis of diethylidene mannitol to the monoethylidene mannitol, already proved to be either 1 : 3- or 2 : 3-ethylidene mannitol, probably the former. This transformation, therefore, proves not only that the diethylidene mannitol is 1 : 3-4 : 6-diethylidene D-mannitol (V), but also that the monoethylidene derivative is 1 : 3-ethylidene D-mannitol (I). Since each of these has been obtained by the hydrolysis of triethylidene mannitol, this compound must be 1 : 3-2 : 5-4 : 6-triethylidene D-mannitol (VI). Thus the condensations of mannitol with acetaldehyde and formaldehyde follow the same pattern inasmuch as each leads to the 1 : 3-2 : 5-4 : 6-derivative (cf. Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 2215). It is interesting, however, that, whereas the 2 : 5-ring is the least stable to acidic hydrolysis in the ethylidene compound, it is the most stable to acetolysis in the methylene derivative (cf. Ness, Hann, and Hudson, *loc. cit.*).

Experimental.

1 : 3-2 : 5-4 : 6-*Triethylidene* D-*Mannitol from Mannitol.*—Triethylidene D-mannitol was prepared from commercial D-mannitol (200 g.) by Bourne and Wiggins's method (*loc. cit.*). The product (205 g., 71·8%) had m. p. 172°, $[\alpha]_D^{18}$ −72·4° (*c*, 2·37 in chloroform) [Found: C, 55·2; H, 7·8%; *M*, *ca.* 235 (Rast, in camphor). Calc. for $C_{12}H_{20}O_6$: C, 55·4; H, 7·7%; *M*, 260]. Meunier (*loc. cit.*) and Bourne and Wiggins (*loc. cit.*) gave m. p. 174° and 172°, respectively, for this compound. Ettel (*Coll. Czech. Chem. Comm.*, 1930, **2**, 457) recorded $[\alpha]_D^{20}$ −72·7° (*c*, 1·00 in chloroform).

Graded Hydrolysis of 1 : 3-2 : 5-4 : 6-*Triethylidene* D-*Mannitol.*—Triethylidene D-mannitol (20·20 g.) was dissolved in a mixture of alcohol (2 l.) and water (100 c.c.) at 70°, cooled to 30° and, after the addition of 5N-hydrochloric acid (210 c.c.), was kept at 30° for 92 hours, before being neutralised with lead carbonate. The lead salts were removed by filtration at 0° and washed with cold 87% alcohol. The combined filtrate and washings were evaporated, leaving a white solid, which was extracted with water (4 × 100 c.c.). The insoluble residue (5·09 g., 25·2%) had m. p. 170—171°, alone and on admixture with the parent triethylidene D-mannitol. Evaporation of the aqueous extracts afforded a white solid (11·90 g.); this was heated under reflux with a mixture of chloroform (20 c.c.) and acetone (20 c.c.), a procedure which was repeated six times. The material which did not dissolve was exhaustively extracted with aqueous acetone (1% water by volume), leaving an insoluble residue from which D-mannitol hexa-acetate (2·10 g., 6·2%) was recovered after acetylation. The solute obtained from the aqueous acetone solution, when crystallised three times from acetone containing a trace of water, gave 1 : 3-*ethylidene* D-*mannitol* (2·09 g., 12·9%), m. p. 163·5—165° (depressed on admixture with D-mannitol), $[\alpha]_D^{19}$ −39·6° (*c*, 0·91 in water) (Found: C, 46·3; H, 7·7. $C_8H_{16}O_6$ requires C, 46·1; H, 7·7%).

The above chloroform–acetone extracts were evaporated and the residual white solid was washed with chloroform (25 c.c.), before being dissolved in acetone (60 c.c.) and introduced into a column of activated alumina, previously saturated with chloroform. After unsuccessful attempts had been made to elute the column with acetone, benzene, and chloroform, severally, eluate fractions showing strong negative rotations were obtained by use of alcohol. These fractions were combined and evaporated to a solid, which, when crystallised twice from absolute alcohol, gave 1 : 3-4 : 6-*diethylidene* D-*mannitol* (2·01 g., 11·1%), m. p. 185—186°, $[\alpha]_D^{14}$ −71·7° (*c*, 2·40 in acetone) (Found: C, 51·6; H, 7·4. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7%). A further quantity (1·8%) of this compound was recovered as its diacetate (m. p. 150—151°, see below) by evaporation of the above chloroform washings and acetylation of the residue.

1 : 3-2 : 5-4 : 6-*Triethylidene* D-*Mannitol from* 1 : 3-4 : 6-*Diethylidene* D-*Mannitol.*—Diethylidene D-mannitol (0·050 g.), paraldehyde (0·15 c.c.), and hydrobromic acid (0·05 c.c.; *d* 1·46) were shaken together for 6 hours. A crystalline precipitate separated, and chloroform was added until this dissolved. The solution was washed with water, sodium hydrogen carbonate solution, and again with water. The extract was dried ($MgSO_4$), filtered, and evaporated to dryness. The residual solid was crystallised twice from alcohol, giving needles (0·027 g., 48·6%), $[\alpha]_D^{23}$ −72·8° (*c*, 0·41 in chloroform), m. p. 171—172° alone or on admixture with 1 : 3-2 : 5-4 : 6-triethylidene mannitol prepared directly from mannitol.

1 : 3-2 : 5-4 : 6-*Triethylidene* D-*Mannitol from* 1 : 3-*Ethylidene* D-*Mannitol.*—1 : 3-Ethylidene mannitol (0·082 g.), paraldehyde (1·0 c.c.), and concentrated hydrochloric acid (0·15 c.c.) were shaken together for 24 hours. The solid product was dissolved by addition of chloroform, and the chloroform layer was treated as above. The product (0·075 g., 73·2%) had m. p. 171—172°, alone or on admixture with 1 : 3-2 : 5-4 : 6-triethylidene mannitol prepared directly from mannitol.

2 : 4 : 5 : 6-*Tetrabenzoyl* 1 : 3-*Ethylidene* D-*Mannitol.*—1 : 3-Ethylidene mannitol (0·300 g.) was treated with benzoyl chloride (1·90 c.c.) in pyridine (12 c.c.) at 18° for 48 hours, before being poured into water and extracted with chloroform. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), filtered, and evaporated to a syrup, which crystallised from aqueous alcohol. Two recrystallisations gave 2 : 4 : 5 : 6-*tetrabenzoyl* 1 : 3-*ethylidene* D-*mannitol* (0·650 g., 72·2%), m. p. 111—112°, $[\alpha]_D^{20}$ +12·8° (*c*, 0·78 in ethyl alcohol) (Found: C, 69·2; H, 5·3. $C_{34}H_{32}O_{10}$ requires C, 69·2; H, 5·2%).

1 : 2 : 5 : 6-*Tetrabenzoyl* 3 : 4-*Ethylidene* D-*Mannitol.*—1 : 2 : 5 : 6-Tetrabenzoyl D-mannitol (0·050 g.; m. p. 117—119°), prepared by Fischer's method (*Ber.*, 1915, **48**, 266), was shaken with paraldehyde (2·0 c.c.) and hydrobromic acid (0·4 c.c.; *d* 1·46) for 16 hours, before being poured into water, and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), filtered, and evaporated. The residual syrup, crystallised 3 times from aqueous alcohol, afforded 1 : 2 : 5 : 6-*tetrabenzoyl* 3 : 4-*ethylidene* D-*mannitol* (0·025 g., 47·9%), m. p. 98—99°.

depressed to 88° on admixture with 2 : 4 : 5 : 6-tetrabenzoyl 1 : 3-ethylidene D-mannitol (Found: C, 69·5; H, 5·3. $C_{36}H_{32}O_{10}$ requires C, 69·2; H, 5·2%).

2 : 4 : 5-*Triacetyl* 1 : 3-*Ethylidene* 6-*Toluene*-p-*sulphonyl* D-*Mannitol*.—1 : 3-Ethylidene mannitol (0·460 g.) was treated with toluene-*p*-sulphonyl chloride (0·421 g., 1 mol.) in pyridine (4·3 c.c.) at room temperature for 48 hours. Acetic anhydride (0·75 c.c.) was added, and the solution was kept at room temperature for another 48 hours, before being poured into water and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), filtered, and concentrated to a syrup, which crystallised from aqueous alcohol. After 3 more crystallisations, the *product* (0·392 g., 36·3%) showed m. p. 122·5—124·5°, $[\alpha]_D^{17}$ +9·5° (*c*, 1·37 in chloroform) (Found: C, 51·2; H, 5·9; S, 6·7. $C_{31}H_{38}O_{11}S$ requires C, 51·6; H, 5·8; S, 6·6%).

Reaction of 2 : 4 : 5-*Triacetyl* 1 : 3-*Ethylidene* 6-*Toluene*-p-*sulphonyl* D-*Mannitol with Sodium Iodide in Acetone*.—When the toluene-*p*-sulphonate (0·273 g.) and excess of sodium iodide were heated in dry acetone (10 c.c.), in a sealed tube, at 100° for 3 hours, sodium toluene-*p*-sulphonate (0·104 g., 95·9%) was precipitated.

1 : 3-*Ethylidene* 2 : 4 : 5 : 6-*Tetratoluene*-p-*sulphonyl* D-*Mannitol*.—Toluene-*p*-sulphonyl chloride (0·90 g., 4·3 mols.) was added to a solution of 1 : 3-ethylidene D-mannitol (0·230 g.) in pyridine (6·0 c.c.), and the mixture was kept at 20° for 48 hours. The syrup which formed when the mixture was poured into water was separated by decantation and dissolved in ether. The ethereal solution was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residual amorphous 1 : 3-*ethylidene* 2 : 4 : 5 : 6-*tetratoluene*-p-*sulphonyl* D-*mannitol* (0·172 g., 18·9%) was dried in a vacuum over phosphoric anhydride (Found: C, 52·7; H, 5·1; S, 15·3. $C_{54}H_{58}O_{14}S_4$ requires C, 52·4; H, 4·9; S, 15·5%). Extraction of the aqueous solution with chloroform afforded a white solid (0·259 g.) which appeared to be mainly tritoluene-*p*-sulphonyl derivatives.

Reaction of 1 : 3-*Ethylidene* 2 : 4 : 5 : 6-*Tetratoluene*-p-*sulphonyl* D-*Mannitol with Sodium Iodide in Acetone*.—The tetratoluene-*p*-sulphonate (0·0558 g.) and sodium iodide (0·205 g.) were heated in dry acetone (15 c.c.) (sealed tube) at 100—110° for 8 hours. The precipitated sodium toluene-*p*-sulphonate (0·0127 g.) represented an exchange of 0·97 ester group per molecule of the mannitol derivative.

Oxidation of 1 : 3-*Ethylidene* D-*Mannitol with Lead Tetra-acetate*.—When 1 : 3-ethylidene D-mannitol ($3·86 \times 10^{-4}$ mole) was oxidised with lead tetra-acetate in glacial acetic acid, according to the method of Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667), the number of moles of oxidising agent consumed per mole of the ethylidene compound was 1·14 (30 mins.), 1·58 (60 mins.), 1·84 (120 mins.), and 1·97 (240 mins.).

Periodate Oxidation of 1 : 3-*Ethylidene* D-*Mannitol*.—(a) *Isolation of formaldehyde*. 1 : 3-Ethylidene D-mannitol ($1·01 \times 10^{-4}$ mole), oxidised under the conditions recommended by Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476), gave, per mole, 0·99 mole of formaldehyde, isolated as its dimedone derivative (m. p. 188°).

(b) *Determination of formic acid*. A solution of 1 : 3-ethylidene D-mannitol ($0·85 \times 10^{-4}$ mole) in water (30 c.c.) was treated with 0·25M-sodium metaperiodate (6 c.c.) at 20° (cf. Hirst and Jones, *J.*, 1949, 1659). At intervals, a portion (5 c.c.) of the solution was removed, and treated with excess of ethylene glycol (0·2 c.c.). Titration with 0·009N-sodium hydroxide, with methyl red as indicator, showed that the number of moles of formic acid liberated per mole of ethylidene mannitol was 1·00 (22 minutes), 0·99 (62 minutes), 1·01 (92 minutes), 1·00 (122 minutes), 1·01 (152 minutes), and 1·03 (895 minutes). The oxidation of ethylidene mannitol at 100° gave much higher yields of formic acid, presumably because the acidity produced during the reaction was sufficient, at the higher temperature, to cause hydrolysis of the acetal, so that, in the presence of excess of periodate, further oxidation ensued.

(c) *Isolation of* 2 : 4-*ethylidene* aldehydo-D-*erythrose*. A solution of sodium metaperiodate (0·98 g., 2·4 mols.) in water (13 c.c.) was added dropwise to an aqueous solution (1·5 c.c.) of 1 : 3-ethylidene D-mannitol (0·399 g.). After the mixture had been kept at 20° for 16 hours, it was neutralised with silver carbonate and filtered. The filtrate was treated with an aqueous solution of barium chloride to precipitate barium iodate and barium metaperiodate (cf. Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1663). After 44 hours the solution was filtered, and freeze-dried in the presence of barium carbonate (0·5 g.). The residue was extracted several times with boiling chloroform, and the solution was filtered and concentrated to a syrup, from which the last traces of solvent were removed at 40°/0·05 mm. The *product* (0·22 g., 78·6%), which restored the colour to decolorised magenta, had n_D^{21} 1·4853, $[\alpha]_D^{20}$ −12·8° (*c*, 4·08 in ethyl alcohol) (Found: C, 49·2; H, 7·0. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%).

(d) *Isolation of* D-*erythrose*. A suspension of 2 : 4-ethylidene *aldehydo*-D-erythrose (0·151 g.) in 0·5N-sulphuric acid (6 c.c.) was kept at 18° for 48 hours and then heated at 70° for 19 hours. The solution was neutralised with barium carbonate and filtered. The filtrate was decolorised with charcoal and evaporated to a syrup (0·102 g., 82·2%), which showed $[\alpha]_D^{15}$ (equilibrium) −17·0° (*c*, 3·39 in water), compared with the value $[\alpha]_D^{15}$ (equilibrium) −18·5° (*c*, 3·24 in water) reported for D-erythrose by Overend, Stacey, and Wiggins (*J.*, 1949, 1358). When the syrup (0·092 g.) was treated with phenylhydrazine, under the usual conditions, it gave D-erythrosazone (0·059 g., 25·8%), m. p. 161—163°. Felton and Freudenberg (*J. Amer. Chem. Soc.*, 1935, **57**, 1637) gave m. p. 160—163° for L-erythrosazone. For the D-isomer, Overend, Stacey, and Wiggins (*loc. cit.*) reported m. p. 160—162·5°.

2 : 5-*Diacetyl* 1 : 3-4 : 6-*Diethylidene* D-*Mannitol*.—Diethylidene mannitol (2·20 g.) was treated with acetic anhydride (8·9 c.c.) in pyridine (35 c.c.) for 48 hours at 18°. The white solid, which separated when the solution was poured into water, was removed by filtration. Recrystallised twice from aqueous alcohol, the *acetate* (1·06 g., 35·5%) had m. p. 150—151°, $[\alpha]_D^{20}$ −87·1° (*c*, 0·62 in acetone) (Found: C, 52·8; H, 6·9; Ac, 26·6. $C_{14}H_{22}O_8$ requires C, 52·8; H, 7·0; Ac, 27·0%). A further quantity (0·28 g., 9·4%) of the product was recovered from the aqueous filtrate by extraction with chloroform.

1 : 3-4 : 6-*Diethylidene* 2 : 5-*Ditoluene*-p-*sulphonyl* D-*Mannitol*.—Diethylidene mannitol (1·272 g.) was treated with toluene-*p*-sulphonyl chloride (2·277 g., 2·2 mols.) in pyridine (10 c.c.) at 20° for 74 hours, before being poured into ice-water (40 c.c.) and extracted with chloroform. The extract was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$), filtered, and concentrated to a syrup, which crystallised readily from absolute alcohol. After three more crystallisations, the *product* (1·659 g., 56·3%) had m. p. 134—135°, $[\alpha]_D^{22}$ −73·0° (*c*, 0·89 in chloroform) (Found: C, 52·9; H, 5·7; S, 11·7. $C_{24}H_{30}O_{10}S_2$ requires C, 53·1; H, 5·6; S, 11·8%).

Treatment of **1 : 3-4 : 6-*Diethylidene* 2 : 5-*Ditoluene*-p-*sulphonyl* D-*Mannitol with Sodium Iodide in Acetone*.**—A solution of the ditoluene-*p*-sulphonate (0·178 g.) and sodium iodide (0·50 g.) in dry acetone was heated in a sealed tube at 100—105° for 6 hours. Sodium toluene-*p*-sulphonate was not deposited. The solution was evaporated, and the residue was extracted with chloroform. The extract was washed with sodium thiosulphate solution and then with water, dried ($MgSO_4$), filtered, and evaporated to a syrup, which crystallised from absolute alcohol, to give diethylidene ditoluene-*p*-sulphonyl mannitol (0·130 g., 73·0%), m. p. 132—133°, alone and on admixture with the starting material.

Treatment of **1 : 3-4 : 6-*Diethylidene* D-*Mannitol with Lead Tetra-acetate*.**—Diethylidene mannitol ($1·09 \times 10^{-4}$ mole), treated according to the procedure of Hockett and McClenahan (*loc. cit.*), consumed no lead tetra-acetate during several hours.

1 : 3-4 : 6-*Diethylidene* 2 : 5-*Dimethyl* D-*Mannitol*.—Diethylidene mannitol (0·775 g.), methyl iodide (5 c.c.), and acetone (5 c.c.) were heated under reflux with silver oxide (3 g.) for 40 hours. The solvents were removed by distillation under diminished pressure and the residue was exhaustively extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and concentrated to a syrup, which was re-treated with methyl iodide (5 c.c.) and silver oxide (3 g.), and the syrupy product isolated as before. Crystallised twice from light petroleum (b. p. 60—80°), it gave prisms of **1 : 3-4 : 6-*diethylidene* 2 : 5-*dimethyl* D-*mannitol*** (0·650 g., 74·9%), m. p. 74—75°, $[\alpha]_D^{18}$ −78·3° (*c*, 2·48 in chloroform) (Found: C, 55·0; H, 8·5; OMe, 24·0. $C_{12}H_{22}O_6$ requires C, 54·9; H, 8·5; OMe, 23·7%).

1 : 3 : 4 : 6-*Tetra-acetyl* 2 : 5-*Dimethyl* D-*Mannitol from* 1 : 3-4 : 6-*Diethylidene* 2 : 5-*Dimethyl* D-*Mannitol*.—Diethylidene dimethyl mannitol (0·453 g.) was stirred at 100° with 1·8N-sulphuric acid until dissolution was complete and a constant optical rotation was achieved. The solution was neutralised with barium carbonate, and the insoluble barium salts were removed by filtration. The filtrate was combined with an acetone extract, obtained by continuous extraction of the barium salts, and the solution was evaporated to a syrup, which was extracted several times with boiling absolute methyl alcohol. Evaporation of the combined extracts, and removal of all residual solvent at 60°/0·05 mm., gave syrupy **2 : 5-*dimethyl* D-*mannitol*** (0·355 g., 97·8%) which could not be crystallised.

The syrup (0·350 g.) was dissolved in acetic anhydride (2·55 c.c.), fused sodium acetate (0·34 g.) was added, and the mixture was heated under reflux for 1·75 hours, before being poured into water and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), filtered, and concentrated to a syrup. After being decolorised with charcoal, the syrup was crystallised twice from alcohol, giving **1 : 3 : 4 : 6-*tetra-acetyl* 2 : 5-*dimethyl* D-*mannitol*** (0·361 g., 57·3%), m. p. 107—108°, $[\alpha]_D^{23}$ +39·5° (*c*, 2·30 in methyl alcohol) (Found: C, 50·8; H, 6·9; OMe, 16·7; Ac, 45·8. $C_{16}H_{26}O_{10}$ requires C, 50·8; H, 6·9; OMe, 16·4; Ac, 45·5%).

2 : 5-*Diacetyl* 3 : 4-iso*Propylidene* 1 : 6-*Ditrityl* D-*Mannitol*.—**3 : 4-*iso*Propylidene** D-mannitol (2·50 g.) was treated with triphenylmethyl chloride (6·27 g., 2 mols.) in pyridine (15 c.c.) at 20° for 62 hours. Acetic anhydride (10 c.c.) was added, and the mixture was then kept at the same temperature for 72 hours (cf. Müller, *loc. cit.*), before being poured into water and extracted with chloroform. The extracts were washed with dilute acid, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$), filtered, and concentrated. The residual syrup, crystallised once from absolute alcohol, and three times from methyl alcohol–acetone, afforded **2 : 5-diacetyl 3 : 4-*iso*propylidene 1 : 6-ditrityl D-mannitol** (4·47 g., 50·2%), m. p. 146—147°, $[\alpha]_D^{18}$ −2·5° (*c*, 6·74 in chloroform) (Found: C, 77·3; H, 6·5; Ac, 11·3. Calc. for $C_{51}H_{50}O_8$: C, 77·4; H, 6·4; Ac, 10·9%). Müller (*loc. cit.*) gave m. p. 143° and stated that the compound was optically inactive.

3 : 4-iso*Propylidene* 1 : 6-*Ditrityl* D-*Mannitol*.—A solution of diacetyl *iso*propylidene ditrityl mannitol (2·478 g.) in absolute methyl alcohol (250 c.c.) containing a trace of sodium was kept at 20° for 48 hours. The solvent was removed by distillation, and a portion (0·100 g.) of the white residue (2·196 g.) was crystallised twice from absolute alcohol, giving **3 : 4-iso*propylidene* 1 : 6-*dityrityl* D-*mannitol*** (0·079 g., 78·3%), m. p. 169·5—171°, $[\alpha]_D^{20}$ +15·5° (*c*, 1·03 in chloroform) (Found: C, 79·6; H, 6·3. $C_{47}H_{44}O_6$ requires C, 79·9; H, 5·6%).

2 : 5-*Dimethyl* 3 : 4-iso*Propylidene* 1 : 6-*Ditrityl* D-*Mannitol*.—The residue (2·090 g.) containing **3 : 4-*iso*propylidene 1 : 6-ditrityl D-mannitol** was dissolved in methyl iodide (14 c.c.), and silver oxide (9 g.) was added. The mixture was heated under reflux for 12 hours. Chloroform was added, and the solid was removed by filtration before being extracted several times with boiling chloroform. The filtered extracts were combined, dried ($MgSO_4$), filtered, and evaporated. The residue (2·049 g.) was submitted to two more treatments with the methylating reagents and isolated as before. The product, crystallised twice from chloroform–light petroleum (b. p. 60—80°), gave **2 : 5-*dimethyl* 3 : 4-iso*propylidene* 1 : 6-*ditrityl* D-*mannitol*** (1·765 g., 81·2%), m. p. 235—236°, $[\alpha]_D^{9}$ +9·5° (*c*, 8·53 in chloroform) (Found: OMe, 8·2. $C_{49}H_{50}O_6$ requires OMe, 8·4%).

1 : 3 : 4 : 6-*Tetra-acetyl* 2 : 5-*Dimethyl* D-*Mannitol from* 2 : 5-*Dimethyl* 3 : 4-iso*Propylidene* 1 : 6-*Ditrityl* D-*Mannitol*.—2 : 5-Dimethyl **3 : 4-*iso*propylidene 1 : 6-ditrityl D-mannitol** (1·500 g.) was dissolved in a mixture of dioxan (50 c.c.) and alcohol (10 c.c.) and, after the addition of 10N-hydrochloric acid (10 c.c.), the solution was heated on a boiling water-bath for 8 hours, the optical rotation then being constant. The cooled solution was neutralised with silver carbonate (15 g.) and filtered. The insoluble

salts were washed with dioxan, and the combined filtrate and washings were evaporated, leaving a solid residue, which was extracted several times with hot water. The filtered extracts were treated with hydrogen sulphide, concentrated to a small volume (5 c.c.), and filtered to remove traces of coagulated silver sulphide. The solution was freed from ionic material by a method similar to that of Consden, Gordon, and Martin (*Biochem. J.*, 1947, **41**, 590) and evaporated to a syrup (0·176 g., 41·0%), which could not be crystallised.

The syrup (0·170 g.) was heated under reflux with acetic anhydride (1·55 c.c.) and fused sodium acetate (0·21 g.) for 2 hours, before being poured into excess of sodium hydrogen carbonate solution and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution and then with water, dried ($MgSO_4$), filtered, and evaporated to a syrup, which crystallised from aqueous alcohol. Three more crystallisations gave 1 : 3 : 4 : 6-tetra-acetyl 2 : 5-dimethyl D-mannitol (0·123 g., 40·2%), m. p. 107—108° alone or on admixture with the specimen mentioned above, $[\alpha]_D^{18}$ +39·9° (*c*, 2·86 in methyl alcohol) (Found : C, 50·9; H, 7·2. $C_{16}H_{26}O_{10}$ requires C, 50·8; H, 6·9%).

2 : 5-*Dimethyl* D-*Mannitol from* 1 : 3 : 4 : 6-*Tetra-acetyl* 2 : 5-*Dimethyl* D-*Mannitol*.—1 : 3 : 4 : 6-Tetra-acetyl 2 : 5-dimethyl mannitol (0·062 g.), derived from 2 : 5-dimethyl 3 : 4-*iso*propylidene 1 : 6-dityrityl D-mannitol, was deacetylated, with a trace of sodium in absolute methyl alcohol (5 c.c.), at 18° for 38 hours, and the solution was evaporated. The residual syrup was dissolved in water, and, after the solution had been " desalted " by the method previously described (cf. Consden, Gordon, and Martin, *loc. cit.*), it was evaporated to a syrup (0·034 g., 98·7%), showing $[\alpha]_D^{17}$ −16·2° (*c*, 0·68 in water) (sample A).

In the same way the other specimen of 1 : 3 : 4 : 6-tetra-acetyl 2 : 5-dimethyl D-mannitol (0·231 g.), prepared from 1 : 3-4 : 6-diethylidene 2 : 5-dimethyl D-mannitol, was converted into syrupy 2 : 5-dimethyl D-mannitol (0·123 g., 95·9%), having $[\alpha]_D^{20}$ −15·9° (*c*, 1·39 in water) (sample B).

Periodate Oxidation of 2 : 5-*Dimethyl* D-*Mannitol*.—(a) *Quantity of oxidising agent consumed.* 2 : 5-Dimethyl mannitol (sample A, $1{\cdot}24 \times 10^{-4}$ mole) was dissolved in water (5 c.c.) and 0·30M-sodium metaperiodate (5 c.c.) was added. The solution was diluted to 50 c.c. and kept at 18°. At intervals, portions (2 c.c.) of the solution were removed, and the residual periodate was estimated by adding solutions of sodium hydrogen carbonate and excess of potassium iodide and titrating the liberated iodine with 0·005N-arsenious oxide, starch being used as the indicator (cf. Jackson, *Organic Reactions*, 1944, **2**, 358, 360; Müller and Friedberger, *Ber.*, 1902, **35**, 2652). The number of moles of oxidising agent consumed by each mole of the mannitol derivative was 1·08 (10 mins.), 1·07 (30 mins.), 1·06 (120 mins.), and 1·10 (960 mins.).

In the same way, it was shown that the number of moles of periodate consumed by the other sample (B) of 2 : 5-dimethyl D-mannitol was 0·92 (15 mins.), 0·94 (30 mins.), 1·01 (120 mins.), and 1·14 (540 mins.).

(b) *Production of formaldehyde.* Each of the samples (A and B) of 2 : 5-dimethyl D-mannitol was oxidised with periodic acid and treated with dimedone, under the conditions recommended by Reeves (*loc. cit.*); in neither case could formaldehyde be detected.

(c) *Production of formic acid.* To 2 : 5-dimethyl D-mannitol (sample A; $6{\cdot}33 \times 10^{-5}$ mole) in water (31 c.c.), 0·30M-sodium metaperiodate (5 c.c.) was added and the mixture was kept at 20° (cf. Hirst and Jones, *loc. cit.*). At intervals, portions (5 c.c.) of the solution were removed, mixed with ethylene glycol (0·2 c.c.), and titrated with 0·010N-sodium hydroxide, methyl-red being used as the indicator. No formic acid was produced for, even after 21 hours, the slightly acid solution required the same quantity of alkali for neutralisation as did a control containing the same components except the mannitol derivative.

A similar result was obtained with the other sample (B) of dimethyl D-mannitol.

1 : 3-*Ethylidene* D-*Mannitol from* 1 : 3-4 : 6-*Diethylidene* D-*Mannitol*.—Diethylidene mannitol (0·472 g.) was dissolved in a mixture of alcohol (38 c.c.) and water (2 c.c.) at 70°. The solution was cooled, and, after 5N-hydrochloric acid (5·5 c.c.) had been added, it was heated at 65° for 35 minutes. The acid was neutralised with lead carbonate; the lead salts were removed by filtration at 0° and washed with cold aqueous alcohol. The filtrate and washings were combined, and evaporated to a white solid, which was heated under reflux with a mixture of chloroform (3 c.c.) and acetone (3 c.c.) for 1 hour. After the extraction had been repeated twice, the filtered extracts were combined and evaporated. The solid residue was heated with boiling chloroform (5 c.c.) for 3 hours; the undissolved material was removed by filtration, and crystallised from absolute alcohol. Recrystallisation from absolute alcohol gave 1 : 3-ethylidene D-mannitol (0·050 g., 11·9%), m. p. 161—162° not depressed on admixture with the monoethylidene mannitol mentioned above.

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603. *Syntheses from Lupinine.*

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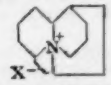
The synthesis of octahydro-1 : 5-*endo*trimethylene- and 1 : 5-*endo*ethylene-octahydro-pyridocolinium salts (V) and (IX) is described. The Hofmann degradation of the former gives two main products, identified as belonging to the aza*bicyclo*[3 : 3 : 1]nonane system (XIII) and the *epi*lupinine series (XII). The latter is formed without any of the lupinine base (XI), which shows that the new ring formed in (V) persists and that the equivalent old ring undergoes fission.

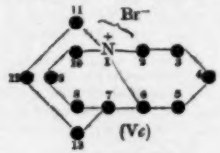
In view of the physiological interest attaching to compounds containing the 1-aza*bicyclo*[3 : 3 : 1]nonane ring system (cf. Badger, Cook, and Walker, *J.*, 1949, 1141; Prelog, Heimbach, and Seiwerth, *Ber.*, 1939, **72**, 1319; McElvain and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 2738) we have examined the possibility of obtaining a compound (XIII) possessing this structure, by the Hofmann degradation of the tricyclic quaternary ammonium bromide (V*a*) prepared from lupinine.

ω-Bromolupinane (Clemo, Raper, and Tenniswood, *J.*, 1931, 429), prepared in improved yield by the use of phosphorus tribromide instead of the pentabromide, condensed with ethyl sodiomalonate to give ethyl ω-lupinylmalonate (I) [Kacnelson and Kabacnik, *Compt. rend. Acad. Sci. U.R.S.S.*, 1936, **13** (4), 409] in good yield. This ester was hydrolysed and decarboxylated by boiling hydrochloric acid, and the resulting monocarboxylic acid esterified with ethanolic hydrogen chloride. Ethyl β-octahydro-1-pyridocolylpropionate (II) was

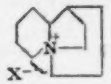
[I; R = $CH(CO_2Et)_2$]
(II; R = $CH_2{\cdot}CO_2Et$)
(III; R = $CH_2{\cdot}CH_2{\cdot}OH$)
(IV; R = $CH_2{\cdot}CH_2Br$)
(VI; R = CN)
(VII; R = CO_2Et)
(VIII; R = $CH_2{\cdot}OH$)



(V*a*; X = Br)
(V*b*; X = Cl)

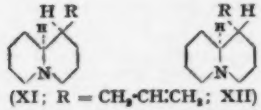


(V*c*)

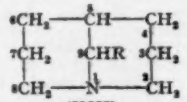


(IX*a*; X = Cl^-)
(IX*b*; X = $C_6H_3O_7N_3^-$)

(X*a*; CH:CH at 9–10)
(X*b*; CH:CH at 1–10)



(XI; R = $CH_2{\cdot}CH{:}CH_2$; XII)



(XIII)

quantitatively reduced to the propanol (III) with lithium aluminium hydride (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197). On treatment with phosphorus tribromide in benzene solution this gave a benzene-soluble basic product, presumably the corresponding propyl bromide (IV), which in boiling benzene cyclised to octahydro-1 : 5-*endo*trimethylene-pyridocolinium bromide (V*a*) {1-azonia*tricyclo*[5 : 3 : 3 : $0^{1,6}$]tridecane bromide (V*c*)}. With thionyl chloride the alcohol (III) yielded the corresponding quaternary chloride (V*b*).

ω-Bromolupinane and sodium cyanide in boiling ethanol gave ω-cyanolupinane (VI) which underwent alcoholysis to ethyl octahydro-1-pyridocolylacetate (VII) on treatment with ethanolic hydrogen chloride. Reduction of this ester with lithium aluminium hydride or with sodium and alcohol gave 2-octahydro-1′-pyridocolylethanol (VIII), which, when treated with thionyl chloride in the same way as its higher homologue, afforded a highly deliquescent crystalline substance, insoluble in non-polar solvents and containing ionic chlorine, thought to be the expected 1 : 5-*endo*ethyleneoctahydropyridocolinium chloride (IX*a*) (1-azonia*tricyclo*-[5 : 3 : 2 : $0^{1,6}$]dodecane chloride). This was converted into the corresponding picrate (IX*b*) for convenience of manipulation.

Hofmann degradation of the quaternary bromide (V*a* = *c*) could theoretically yield five products. Two of these (X*a* and *b*) possess non-terminal double bonds; (XIII) belongs to the 1-azabi*cyclo*[3 : 3 : 1]nonane system; and (XI) and (XII) are based on the octahydropyridocoline system, one belonging to the lupinine, the other to the *epi*lupinine series. (The stereochemical relation between the two series has been adequately discussed by Schöpf, Schmidt, and Braun, *Ber.*, 1931, **64**, 683).

Hofmann degradation of the bromide (V*a* = *c*) produced a mixture, which under ordinary conditions gave an inseparable mixture of picrates melting at approx. 110—120°; but if the picrate preparation was carried out as described in the Experimental section, the base "A" present in maximum amount was obtained as a picrate, m. p. 114°, and the second major constituent "B" as a picrate, m. p. 132—133°; a third picrate, m. p. 140°, was isolated from the mother-liquors, but in insufficient amount for the examination of the base concerned; and even then the final picrate fraction is a mixture. The relative amounts of the bases "A" and "B" are not greatly changed by heating the bromide (V*a*) with potassium hydroxide in water or ethylene glycol instead of using the silver oxide method.

Ozonolysis of bases "A" and "B" showed the presence of a methylene group, a result confirmed by the infra-red spectra (kindly determined for us by Dr. Plíva of the Central Chemical Research Institute, Prague, Czechoslovakia). It was thus evident that "A" and "B" had two of the three structures (XI), (XII), and (XIII).

Quantitative hydrogenation readily gave the dihydro-bases which were different from the base obtained by the replacement of the bromine atom in (IV) by hydrogen, and this indicated that neither "A" nor "B" belonged to the lupinine series (XI).

Oxidation of "A" and "B" was next examined with a view to converting their $\cdot CH{:}CH_2$ groups into carboxyl and thence into carbethoxyl, whereby either "A" or "B" was expected to give the known ethyl *epi*octahydro-1-pyridocolylacetate (cf. VII). Potassium permanganate oxidised "A" smoothly in acetone, and a good yield of ester was obtained from the resulting acid, but its picrate differed from that of the *epi*-ester (VII). Thus structure (XIII) was indicated for "A". Similar oxidation of "B", however, did not proceed satisfactorily and no definite ester could be obtained from the resulting acid, but eventually, as described in the Experimental section, "B" was oxidised successfully with permanganate and the *epi*-ester was obtained. Thus "B" has the structure (XII).

Unexpected difficulty was experienced in obtaining compounds of the *epi*lupinine series. Krieg (Inaug. Diss., Marburg, 1928; cf. *Biedermanns Zentr.*, 1932, **3**, *A*, 51) states that lupinine is quantitatively converted into *epi*lupinine when heated under reflux in benzene with sodium for 3 days. This experiment has been quoted several times (Winterfeld and Holschneider, *Ber.*, 1931, **64**, 137; Schöpf, Schmidt, and Braun, *ibid.*, p. 692; Hückel and Naab, *ibid.*, p. 2137), but apparently not repeated. In our hands this method did not prove satisfactory. Only in one run out of eight was crystalline *epi*lupinine (m. p. 74—76°) obtained, in 10% yield. It is also stated by Winterfeld and Holschneider (*loc. cit.*) that Bouveault–Blanc reduction of methyl lupinate yields *epi*lupinine, but no experimental details or yields are given. We have found that this reaction yields a mixture of lupinine and *epi*lupinine, containing about 40% of the latter. It proved most convenient to convert the mixture into the mixed ω-bromo- and ω-cyano-lupinane epimers, and to effect separation by crystallisation of the ω-cyanolupinane picrates. ω-*epi*Cyanolupinane picrate was thus obtained in 10% yield. The ω-*epi*cyanolupinane recovered from the picrate was converted into ethyl *epi*octahydro-1-pyridocolylacetate. It may be noted that Krieg (*loc. cit.*) regards lupinine as the stable, and *epi*lupinine as the metastable, epimer.

Experimental.

ω-Bromolupinane.—The following modification was found more convenient than the original method [Clemo, Raper, and Tenniswood (*loc. cit.*)]. Lupinine (33 g.) and phosphorus tribromide (10 ml.) in benzene (100 ml.) were refluxed 2 hours, the excess of tribromide decomposed with ice-water, potassium hydroxide (75 g.) in water (300 ml.) added with cooling, the benzene layer separated, and the aqueous layer extracted with benzene. The combined benzene layers were dried (KOH), evaporated, and distilled, giving the bromide (38·1 g., 82%), b. p. 104°/1 mm., which yielded a *picrolonate*, golden yellow plates, m. p. 198—199° (Found: C, 48·8; H, 5·5. $C_{10}H_{18}NBr,C_{10}H_8O_5N_4$ requires C, 48·4; H, 5·3%). Use of less phosphorus tribromide gave lowered yields.

Ethyl Lupinylmalonate.—Ethyl malonate (7·9 g.) was added to sodium ethoxide in boiling ethanol [from sodium (1·2 g.) and alcohol (35 ml.)], and bromolupinane (11·4 g.) was stirred in. Boiling was continued overnight, the ethanol distilled off, the residue taken up in water, basified with 20% aqueous sodium hydroxide, and extracted with ether, and the extract dried, evaporated, and fractionated. Ethyl lupinylmalonate distilled as a clear viscous liquid (11 g., 72%), b. p. 175—178°/3 mm. (Kacnelson and

Kabačnik, *loc. cit.*, gave b. p. 199·5—200°/11 mm.) (Found : C, 65·8; H, 9·5. Calc for $C_{17}H_{19}O_4N$: C, 65·6; H, 9·3%). It afforded a *methiodide*, white prisms (from acetone–ether), m. p. 149—150° (Found : C, 47·7; H, 6·8. $C_{17}H_{19}O_4N,CH_3I$ requires C, 47·7; H, 7·1%). The use of chlorolupinane in this condensation (Kacnelson and Kabačnik, *loc. cit.*) gave a much lower yield.

Ethyl β-Octahydro-1-pyridocolylpropionate.—Ethyl lupinylmalonate (10 g.) was refluxed with hydrochloric acid (75 ml.; 1 : 1) for 5 hours, the solution taken to dryness, and the residual clear yellow gum dissolved in absolute ethanol (75 ml.), and the solution saturated with hydrogen chloride at room temperature and refluxed for 2 hours. The ethanol was distilled off and the residue taken up in water, basified with 20% sodium hydroxide solution, and extracted with ether. The extract was dried, evaporated, and distilled. The *ester* (6 g., 77%), a clear oil, b. p. 136—140°/2 mm. (Found : C, 70·4; H, 10·7. $C_{14}H_{25}O_2N$ requires C, 70·3; H, 10·5%), gave a *methiodide*, m. p. 109—111° (Found : C, 47·3; H, 7·3; N, 6·2. $C_{14}H_{25}O_2N,CH_3I$ requires C, 47·2; H, 7·3; N, 5·9%).

3-Octahydro-1′-pyridocolylpropanol.—Ethyl β-octahydro-1-pyridocolylpropionate (6 g.) in dry ether (20 ml.) was run dropwise into a stirred ethereal solution of lithium aluminium hydride (25 ml., equiv. to 1500 ml. of hydrogen), the solution set aside at room temperature overnight, and water cautiously added to decompose the excess of reagent and then sulphuric acid (20%) till the aqueous layer became clear. The solution was basified (as above) and extracted with ether, and the extract dried and evaporated. *3-Octahydro-1′-pyridocolylpropanol* (4·5 g., 93%) distilled as a colourless viscous oil, b. p. 134—136°/2 mm. (Found : N, 7·3. $C_{12}H_{23}ON$ requires N, 7·1%). It afforded a *methiodide*, white prisms (from methanol), m. p. 184° (Found : C, 46·4; H, 8·0. $C_{12}H_{23}ON,CH_3I$ requires C, 46·0; H, 7·7%).

Octahydro-1 : 5-endotrimethylenepyridocolinium Bromide (*1-Azoniatricyclo*[5 : 3 : 3 : $0^{1,5}$]*tridecane Bromide*).—3-Octahydropyridocolylpropanol (4·5 g.) in benzene (50 ml.) was treated with phosphorus tribromide (6·5 g.; *d* 2·85) and refluxed for 2 hours. Ice-water (30 ml.) was added to the cooled solution, followed by 25% sodium hydroxide solution until the mixture was strongly alkaline. The benzene layer was separated, the aqueous layer was extracted twice more with benzene, and the benzene layers were united, filtered, and evaporated to dryness. During evaporation the quaternary *bromide* was deposited as white needles (4·2 g., 70%). Crystallised from ethanol or ethanol–acetone, it had m. p. 316° (decomp.), $[\alpha]_D^{18}$ −15·53° (*c*, 7·78 in ethanol) (Found : C, 55·3; H, 8·5. $C_{13}H_{22}NBr$ requires C, 55·4; H, 8·5%).

Thionyl chloride, without a solvent or in benzene, gave the corresponding quaternary *chloride*, m. p. 318° (decomp.) (Found : C, 66·7; H, 10·1. $C_{13}H_{22}NCl$ requires C, 66·8; H, 10·2%).

Octahydro-1-n-propylpyridocoline.—3-Octahydro-1′-pyridocolylpropanol (0·7 g.) was converted into the bromide as described above; to the benzene solution was added zinc dust (2 g.) and glacial acetic acid (1 ml.). The mixture was refluxed for 6 hours, the solution separated from the zinc, which was extracted with a little benzene, and the benzene solution shaken with 25% aqueous sodium hydroxide, dried, and fractionated, giving *octahydro-1-n-propylpyridocoline* (0·35 g.), b. p. *ca.* 75°/1 mm. (Found : C, 79·2; H, 12·65. $C_{12}H_{23}N$ requires C, 79·6; H, 12·7%). The *picrate*, made in, and crystallised from, ether, formed compact, deep yellow prisms, m. p. 98—99° (Found : C, 52·9; H, 6·4. $C_{12}H_{23}N,C_6H_3O_7N_3$ requires C, 52·7; H, 6·3%). In addition, a trace of a picrate was obtained as thin, yellow prisms, m. p. 204—205°, sparingly soluble in alcohol (Found : C, 46·7; H, 5·0%).

Degradation of the Quaternary Bromide : Bases " A " and " B ".—The bromide (0·8 g.) was mixed with potassium hydroxide (1·5 g.) and water (1 c.c.) in a small Claisen flask fitted with a dropping funnel and condenser arranged to deliver the distillate into concentrated hydrochloric acid (3 ml.) and water (1 ml.) in a receiver which was connected to a water-pump. The flask was heated in a metal-bath at 245—250°, water and a basic oil being collected in the acid. Water (10 ml.) was dropped in during about 40 minutes, at the end of which no more oil distilled over. The acid solution was taken to dryness under reduced pressure, potassium hydroxide (4 g.) in water (5 ml.) was added, and the liberated bases were extracted with ether (5 times), dried (K_2CO_3), and distilled, giving mixed bases (0·45 g.), b. p. 127°/30 mm.

Picrates of " A " and " B ".—To the above bases (0·45 g.) in ether (3·5 ml.), a hot solution of picric acid (0·6 g.) in ethyl acetate (3·5 ml.) was added cautiously. After a few minutes, long, pale yellow prisms (*P*) began to separate, which amounted to 0·46 g., m. p. 110—112°, after 2 hours. By recrystallisation from ethyl acetate by the addition of an equal volume of ether, or from ethyl alcohol (10 ml.), the m. p. of this *picrate* of base " *A* " was raised to 114° (Found : C, 52·6; H, 5·8. $C_{12}H_{21}N$, $C_6H_3O_7N_3$ requires C, 52·9; H, 5·9%).

The filtrate from (*P*) was concentrated (to 2 ml.), and ether (2 ml.) added to the solution, which was then set aside, whereupon the picrate of " *B* " usually separated spontaneously; if it did not a seed was added and after 1 hour's storage at laboratory temperature, followed by ice-cooling for a few minutes, stout prisms (0·18 g.) were obtained, having m. p. 129—130°. On recrystallisation from ethyl acetate by the addition of an equal volume of ether the m. p. of this *picrate* of base " B " rose to 134° (Found : C, 52·8; H, 6·2%).

When the filtrate from the fraction of b. p. 129—130° was set aside in the refrigerator for one night, a further 0·1 g. of product separated, which melted at 100—110°; and from some batches of which a small amount of deep golden prisms, m. p. 140—141° (from ethanol) was obtained (Found : C, 52·4; H, 6·1%).

9-But-3′-enyl-1-azabicyclo[3 : 3 : 1]*nonane* (*Base " A "*) (XIII).—The picrate, m. p. 114° (1·5 g.), was suspended in a solution of sodium hydroxide (5 g.) in water (10 ml.) and steam-distilled. The oily distillate was acidified (hydrochloric acid), taken to dryness, basified with potassium hydroxide (3 g. in water, 4 ml.), extracted with ether, dried (K_2CO_3), and distilled, giving *base* " A " (0·57 g.), b. p. 115°/15 mm. (Found : C, 80·7; H, 12·1. $C_{12}H_{21}N$ requires C, 80·4; H, 11·7%). The *methiodide* formed colourless well-formed prisms (from acetone), m. p. 232—233° (Found : C, 49·3; H, 7·5. $C_{12}H_{21}N,CH_3I$

requires C, 48·6; H, 7·5%). On catalytic reduction in 10% sulphuric acid over palladised charcoal at atmospheric pressure, the theoretical amount of hydrogen was absorbed in 45 minutes and the dihydro-base obtained (Found: C, 79·7; H, 12·65. $C_{13}H_{23}N$ requires C, 79·6; H, 12·7%). 9-n-*Butyl*-1-*aza*-bicyclo[3 : 3 : 1]*nonane* is stable indefinitely and forms a *picrate*, made in, and crystallised from, ether as long yellow prisms (Found: C, 53·0; H, 6·55. $C_{13}H_{23}N,C_6H_3O_7N_3$ requires C, 52·7; H, 6·3%), m. p. 84—85°, depressed to 75° by admixture with picrate of octahydro-3-*n*-propyl pyridocoline).

Oxidation. Base "A" (0·57 g.) in acetone (15 ml.) was cooled in ice and stirred, whilst powdered potassium permanganate (1·62 g.) was added during 2 hours. The stirring was continued for 4 hours, the mixture left overnight and filtered, and the manganese oxide precipitate extracted with boiling water. The aqueous extract was taken to dryness and esterified by refluxing it for 2 hours in ethyl alcohol (10 ml.) which had been saturated when ice-cold with dry hydrogen chloride. The alcoholic solution was then evaporated to dryness, saturated aqueous potassium carbonate added, and the liberated ester extracted with ether and distilled, giving 9-3′-*carboxypropyl*-1-*aza*bicylo[3 : 3 : 1]*nonane* (0·38 g.), b. p. 125°/1 mm. (Found: C, 69·15; H, 10·1. $C_{13}H_{23}O_2N$ requires C, 69·3; H, 10·2%). The derived *picrate* formed yellow prisms (from ether), m. p. 75—76° (Found: C, 49·95; H, 5·9. $C_{13}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 50·2; H, 5·7%). [In the first oxidation experiment, the picrate obtained had m. p. 98—99° (Found: C, 50·7; H, 5·9%), but in all others the picrate, m. p. 75—76°, was obtained; their relation remains obscure]. The *methiodide*, colourless prisms from acetone, had m. p. 125° (Found: C, 45·8; H, 7·4. $C_{13}H_{23}O_2N,CH_3I$ requires C, 45·8; H, 7·1%).

The epi*Lupinine Base "B"* (epi-1-*Allyloctahydropyridocoline*).—This *base* was regenerated from the picrate as for base "A", and had b. p. 123°/22 mm. (Found: C, 80·2; H, 12·2. $C_{13}H_{21}N$ requires C, 80·4; H, 11·7%). Reduction, as for "A," gave the *dihydro-base* which decomposed when kept (Found: C, 79·05; H, 12·75. $C_{13}H_{23}N$ requires C, 79·6; H, 12·7%). The *picrate*, well-formed rhombs from ether, had m. p. 131—132°, depressed to 117—120° on admixture with the picrate of "*B*" (Found: C, 52·7; H, 6·2. $C_{13}H_{23}N,C_6H_3O_7N_3$ requires C, 52·7; H, 6·3%).

Oxidation. The base (100 mg.), dissolved in 10% sulphuric acid (5 ml.) was treated with aqueous potassium permanganate at room temperature for 2 days, until the supernatant liquid remained pink; about 0·2 g. of permanganate was required. The manganese oxide precipitate was filtered off and extracted twice with hot water, and the combined filtrate and extracts were neutralised with aqueous ammonia and evaporated to dryness. The residue was evaporated twice with ethanol and then extracted with boiling absolute ethanol (4 × 5 ml.). The extracts were evaporated to half-volume and saturated with gaseous hydrogen chloride at room temperature, and the solution refluxed for 2 hours, taken to dryness in a vacuum on the water-bath. The residue was taken up in water (3 ml.), excess of potassium carbonate added, and the base extracted with ether. The extract was dried (Na_2SO_4) and evaporated, and the residue distilled; it had b. p. 80—90° (air-bath temp.) at 0·05 mm. The yield was 30 mg. The *picrate* formed bright yellow prisms (from ethanol), m. p. 137—138°, alone or mixed with ethyl *epi*octahydro-1-pyridocolylacetate picrate (Found: C, 49·95; H, 5·8; $C_{13}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 50·2; H, 5·7%).

Ozonolysis of Bases "A" and "B".—Base "A" (0·2 g.) in purified chloroform (10 ml.) was cooled in ice-salt, a 6% stream of ozone passed in for 4 hours, and the whole left overnight. The chloroform was removed in a vacuum, water (10 ml.) added to the residue, and the resulting solution heated in a Claisen flask for 1 hour on the water-bath and then distilled into an alcoholic solution of dimedone. More water (20 ml.) was gradually dropped in and distilled off. Next morning the crystalline dimedone condensation product was collected; it (0·05 g.) had m. p. 186—187°.

Base "B" gave a similar result.

ω-Cyanolupinane.—ω-Bromolupinane (5 g.) was heated under reflux overnight with potassium cyanide (2 g.) in ethanol (40 ml.), the ethanol distilled off, the residue taken up in water and extracted with ether, the extract dried and evaporated, and the *ω-cyanolupinane* distilled; it (3·85 g., 90%) had b. p. 108—112°/1 mm. (Found: C, 73·9; H, 10·5. $C_{11}H_{18}N_2$ requires C, 74·2; H, 10·1%). It gave a *picrate* m. p. 150—151° (Found: C, 50·0; H, 4·7. $C_{11}H_{18}N_2,C_6H_3O_7N_3$ requires C, 50·1; H, 5·2%), and a *methiodide*, white prisms (from methanol), m. p. 241—242° (Found: C, 45·3; H, 6·7. $C_{11}H_{18}N_2,CH_3I$ requires C, 45·0; H, 6·6%).

Ethyl Octahydro-1-pyridocolylacetate.—ω-Cyanolupinane (7·6 g.) was dissolved in absolute ethanol (150 ml.), and the solution was saturated with hydrogen chloride at room temperature and refluxed overnight. The solution was worked up as described for ethyl β-octahydro-1-pyridocolylpropionate. *Ethyl octahydro-1-pyridocolylacetate* (6 g., 62%) distilled as a colourless oil, b. p. 125—129°/3 mm. (Found: C, 68·9; H, 10·6. $C_{13}H_{23}O_2N$ requires C, 69·3; H, 10·2%). Its *picrate*, yellow needles, had m. p. 202—203° (Found: C, 50·1; H, 5·6. $C_{13}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 50·2; H, 5·7%).

2-Octahydro-1′-pyridocolylethanol.—(*a*) Ethyl octahydro-1-pyridocolylacetate (406 mg.) in ether (5 ml.) was added to excess of ethereal lithium aluminium hydride (5 ml., equiv. to 275 ml. of hydrogen). The solution was refluxed for 1 hour, cooled, and worked up as described for 3-octahydro-1′-pyridocolylpropanol. The *2-octahydro-1′-pyridocolylethanol* (350 mg., 97%) distilled as a clear viscous liquid at 120—130°/2 mm. (air-bath temp.) (Found: C, 71·8; H, 11·6. $C_{11}H_{21}ON$ requires C, 72·1; H, 11·5%) and gave a *methiodide* as white needles (from methanol), m. p. 205—207° (Found: C, 44·4; H, 7·6. $C_{11}H_{21}ON,CH_3I$ requires C, 44·3; H, 7·4%).

(*b*) To ethyl pyridocolylacetate (5·4 g.) in boiling absolute ethanol (150 ml.), sodium (10 g.) was added and refluxing continued until all the sodium had reacted. The solution was cooled, water (300 ml.) added with cooling, and the solution acidified (20% sulphuric acid). 250 ml. were distilled off in a vacuum. The residue was basified with 20% aqueous sodium hydroxide and extracted with ether, and the extract dried and evaporated. The alcohol (2·4 g., 55%) distilled at 124—125°/2 mm.

1 : 5-endo*Ethyleneoctahydropyridocolinium Picrate* (1-*Azoniat*ricyclo[5 : 3 : 2 : $0^{1:6}$]*dodecane Picrate*).—A solution of the foregoing alcohol (1 g.) in benzene (15 ml.) was treated with thionyl chloride (3 ml.), then refluxed for 15 minutes, the benzene and excess of thionyl chloride were distilled off, the residue was taken up in water and filtered, and the filtrate basified with 20% aqueous sodium hydroxide and extracted with benzene. Evaporation of the solvent left a brown oil, insoluble in benzene or ether, which partly crystallised under acetone. It was boiled with charcoal in ethanol, and the solution evaporated to 1 ml. Ether (5 ml.) was added, and the deliquescent precipitate collected. It contained ionic chlorine, was combustible, and was considered to be the expected 1 : 5-*endo*ethyleneoctahydropyridocolinium chloride. As it was very hygroscopic, it was converted, in ethanol, into the *picrate* (90 mg., 4·5%), which was soluble in cold water, but crystallised from absolute ethanol, and decomposed at 253—257° (Found: C, 52·2; H, 6·0. $C_{11}H_{19}N,C_6H_3O_7N$ requires C, 51·8; H, 5·6%).

Reduction of Methyl Lupinate.—Methyl lupinate (6·2 g.) (Schöpf, *Annalen*, 1928, **465**, 108; Willstätter and Fourneau, *Ber.*, 1902, **31**, 1917), reduced by sodium in alcohol as described for ethyl octahydro-1-pyridocolylacetate, yielded a viscous oily mixture (4 g., 85%) of lupinine and *epi*lupinine which did not solidify on being seeded with lupinine. The specific rotation of the mixture ($[\alpha]_D^{18}$ +0·8°; *c*, 10·7 in absolute ethanol) indicated that the mixture contained 40% of *epi*lupinine, if the values for the rotations of the two epimers given by Winterfeld and Holschneider (*loc. cit.*) are accepted.

ω-epi*Cyanolupinane.*—The procedure described for the preparation of ω-bromolupinane yielded a mixture of ω-bromolupinane epimers (4 g., 73%) from the mixed lupinine epimers. Treatment of this with sodium cyanide (8 g.) in boiling ethanol (30 ml.) and working up the product by the method described for ω-cyanolupinane gave the mixed ω-cyanolupinane epimers, (2·6 g., 90%), b. p. 118—122°/2 mm. This mixture with picric acid (2·6 g.) in ethanol (50 ml.) gave mixed picrates (3·7 g.), m. p. 135—140°, clear at 165°. Fractional crystallisation from ethanol yielded ω-epi*cyanolupinane picrate* (0·46 g., 10%), m. p. 207—208° (Found: C, 50·2; H, 5·2. $C_{11}H_{18}N_2,C_6H_3O_7N_3$ requires C, 50·1; H, 5·2%). This (245 mg.) was ground with hydrochloric acid (5 ml.; 1 : 1), the picric acid filtered off, the filtrate washed with ether, basified with 20% aqueous sodium hydroxide, and extracted with ether, and the dried extract evaporated. ω-epi*Cyanolupinane* (98 mg., 91%) distilled at 120—125°/2 mm. (air-bath temp.) (Found: C, 74·2; H, 10·3. $C_{11}H_{18}N_2$ requires C, 74·2; H, 10·1%).

Ethyl epi*Octahydro-1-pyridocolylacetate.*—ω-*epi*Cyanolupinane (98 mg.) was refluxed with saturated alcoholic hydrogen chloride (10 ml.) overnight and the solution worked up as described for ethyl octahydro-1-pyridocolylacetate. The *epi*-ester (53 mg., 43%) had b. p. 120—122°/2 mm. (air-bath temp.) (Found: C, 69·2; H, 10·5. Calc. for $C_{13}H_{23}O_2N$: C, 69·3; H, 10·2%) and gave a picrate, yellow needles (from alcohol), m. p. 136—137° not depressed by admixture of the picrate of the ester obtained by the oxidation of base "B".

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604. *The Influence of Mixed Solvents on the Dissociation Constant of Silver Acetate.*

By P. B. DAVIES and C. B. MONK.

By means of the solubility of silver bromate in various organic solvent–water mixtures containing sodium acetate, the variations in the dissociation constant of silver acetate with changing dielectric constant have been followed. These variations are influenced by the nature of the organic solvent. The results have been used to interpret the solubility of silver acetate in various solvents.

WHILE the influence of solvents of varying dielectric constants on the extent of ionisation of electrolytes has a qualitative explanation, there is still no adequate theoretical treatment which can rigidly account for the observed variations. Consequently it would be useful to compare experimental results with the theoretical interpretations. So far as salt solutions are concerned, however, there is very little available material. Hogge and Garrett (*J. Amer. Chem. Soc.*, 1941, **63**, 1089) developed a solubility method to find the dissociation constant of thallous chloride in ethanol–water solutions; Black and Garrett (*ibid.*, 1943, **65**, 862) studied the same salt in glycol–water; and James (*ibid.*, 1949, **69**, 110) used available data to calculate the extent of dissociation of lead chloride in glycol–water, and later (*J.*, 1950, 1094; 1951, 153) reported conductivity results from which the dissociation constants of lanthanum ferricyanide, of copper sulphate, and of zinc sulphate and malonate in four different types of solvents were found. In the present paper we report results for the ionisation of silver acetate in six different types of organic solvent–water mixtures, obtained by measuring the solubility of silver bromate in these

solvents in the presence of sodium acetate, an excess of acetic acid being used to suppress hydrolysis.

Experimental.

Silver bromate was prepared, and the solubilities (at 25° ± 0·03°) were obtained, as described elsewhere (Monk, *Trans. Faraday Soc.*, 1951, **47**, 292). The organic solvents used were of laboratory grade except in the case of dioxan (AnalaR). Sufficient excess of AnalaR acetic acid was added to the solvent mixtures after the addition of sodium hydroxide to keep the pH at 5—6. The solubilities are reported in Table II. In most cases the exact composition of the solvents, *i.e.*, the proportion of organic solvent, was found by determination of the solubility in the solvent mixture alone and interpolation from available data (Owen, *J. Amer. Chem. Soc.*, 1933, **55**, 1922; Neuman, *ibid.*, 1934, **56**, 28), but in a few cases these were supplemented by density measurements. Dielectric constants were obtained from Akerlof's data (*ibid.*, 1932, **54**, 4125).

Discussion.

For purposes of calculation, a general form of activity-coefficient expression was derived from that given by Davies (*J.*, 1938, 2093) for aqueous solutions at 25°, *i.e.*,

$$-\log f_{\pm} = 0{\cdot}5\,[I/(1 + I^{\frac{1}{2}}) - 0{\cdot}2\,I]$$

by modifying it to the form

$$-\log f_{\pm}^2 = (78{\cdot}54/D)^{3/2}[I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) - 0{\cdot}2I] = F'(I)$$

where 78·54 is the dielectric constant of water (Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," New York, 1943, p. 118), D is the dielectric constant of the solvent, and I is the ionic strength. The following expressions were also used:

$$\log [Ag^+][BrO_3'] - F'(I) = \log S_0$$
$$\log [AgBrO_3] = \log [Ag^+][BrO_3'] - \log K_1 - F'(I)$$
$$\log [NaBrO_3] = \log [Na^+][BrO_3'] - \log K_2 - F'(I)$$
$$[OAc'] = [Ag^+] + [Na^+] - [BrO_3']$$
$$\log K = \log [Ag^+][OAc'] - \log [AgOAc] - F'(I)$$

where S_0 is the solubility product of silver bromate, and K, K_1, and K_2 are dissociation constants. In water, K_1 may be taken as 0·5 by analogy with silver perchlorate ($K_1 = 0{\cdot}6$) (Monk, *J. Amer. Chem. Soc.*, 1948, **70**, 3281) and K_2 is 3·8 (Banks, Righellato, and Davies, *Trans. Faraday Soc.*, 1931, **27**, 621), but these will be different in the mixed solvents. As an approximation it has been assumed that they vary at the same rate that the dissociation constant of silver acetate varies, *i.e.*, after preliminary values of K were obtained, K_1 and K_2 were modified by the ratio K(solvent)/K(water).

To illustrate that the activity-coefficient expression and the assumptions concerning the variations of K_1 and K_2 with D are reasonably correct, some data of Davis, Ricci, and Sauter (*J. Amer. Chem. Soc.*, 1939, **61**, 3274) for the solubility of silver acetate in 10% dioxan–water containing sodium nitrate have been used to calculate S_0 values by using the value of K obtained by interpolation from the results given in Table II. K was then found to alter from 0·23 in water to 0·14 in this solvent, so that the dissociation constants of sodium nitrate and silver nitrate have been altered from 3·8 in water (Davies, *Trans. Faraday Soc.*, 1927, **23**, 351) to 2·2, and from 1·5 in water (Davies, *Endeavour*, 1945, **4**, No. 15) to 0·88, respectively. These calculations are shown in Table I, where the concentrations are expressed in millimols. and mg.-ions per l. S represents the solubility of silver acetate. The constancy of S_0 over an ionic strength of 0·1 (the limit of the original activity expression) supports the assumptions made.

Table I.

Solubility of silver acetate in 10% *dioxan-water.*

$NaNO_3$	S	$[Ag^+]$	$[OAc']$	[AgOAc]	$[NaNO_3]$	$[AgNO_3]$	10^3I	$-\log S_0$
—	50·32	41·97	41·97	8·37	—	—	41·97	2·947
5·08	50·81	42·32	42·47	8·34	0·01	0·15	47·47	2·949
9·92	51·16	42·56	42·84	8·32	0·03	0·28	52·30	2·950
49·79	54·13	44·47	45·81	8·32	0·58	1·34	93·63	2·949

In Table II, the dissociation constant of silver acetate obtained in a number of mixed solvents is recorded. The values were obtained by an approximation method by using the expressions quoted above. The average results are plotted as log K against D in Fig. 1, from which it is

TABLE II.

Silver bromate solubilities.

(All figures, $\times 10^{-3}$; S_A = solubility in the mixed solvent; S_B = solubility in the same solvent containing sodium acetate.)

S_A	S_B	NaOH	HOAc	[Ag$^+$]	[$AgBrO_3$]	[$NaBrO_3$]	[OAc$^-$]	[AgOAc]	10^3I	K
				Water, D = 78·54.						
8·11	9·28	31·80	54·18	8·41	0·11	0·05	31·04	0·76	40·15	0·238
	9·54	39·75	45·01	8·41	0·11	0·07	38·73	1·02	48·09	0·216
	10·24	71·52	77·60	8·51	0·11	0·12	69·90	1·62	79·91	0·230
				43·5% Methanol, D = 59·3.						
1·58	2·13	19·53	22·72	1·57	0·03	0·04	19·00	0·53	21·06	0·037
	2·35	31·25	37·86	1·57	0·03	0·07	30·50	0·75	32·75	0·038
	2·47	39·06	56·79	1·56	0·03	0·08	38·18	0·88	40·54	0·039
				53·8% Methanol, D = 54·6.						
1·09	1·58	19·53	22·72	1·08	0·02	0·04	19·05	0·48	20·57	0·026
	1·78	31·25	35·63	1·07	0·02	0·07	30·56	0·69	32·25	0·027
	1·84	35·15	41·65	1·07	0·02	0·08	34·40	0·75	36·14	0·027
				29·5% Ethanol, D = 61·8.						
2·69	3·86	39·06	45·44	2·68	0·05	0·10	37·93	1·13	41·64	0·053
	4·28	66·36	67·00	2·69	0·05	0·15	57·02	1·54	61·10	0·054
				40·6% Ethanol, D = 54·7.						
1·86	3·05	39·06	45·44	1·84	0·04	0·11	37·89	1·17	40·79	0·032
	3·20	46·87	53·01	1·84	0·04	0·13	45·56	1·32	48·59	0·032
				52·2% Ethanol, D = 47·7.						
1·14	1·88	19·53	22·72	1·07	0·03	0·08	18·75	0·78	20·52	0·014
	2·25	35·15	41·66	1·07	0·03	0·15	33·99	1·15	36·06	0·015
				21·1% Acetone, D = 65·7.						
3·98	4·94	25·26	38·37	4·07	0·09	0·06	24·46	0·78	29·29	0·084
	5·37	42·10	51·80	4·11	0·09	0·13	40·93	1·17	46·07	0·087
				26·1% Acetone, D = 60·5.						
3·18	4·32	29·72	57·90	3·21	0·07	0·09	28·68	1·04	32·83	0·054
	4·67	41·28	80·88	3·17	0·07	0·12	39·85	1·43	44·33	0·050
	5·19	63·91	123·6	3·16	0·07	0·19	61·95	1·96	66·88	0·052
				38·4% Acetone, D = 55·6.						
2·16	3·18	25·26	34·53	2·09	0·05	0·08	24·24	1·04	27·29	0·029
	3·70	42·10	50·84	2·03	0·05	0·15	40·48	1·62	43·98	0·027
				39·5% Acetone, D = 54·9.						
2·07	3·51	37·05	72·37	1·93	0·06	0·16	35·53	1·52	38·82	0·024
	3·62	41·28	80·88	1·93	0·06	0·17	39·65	1·63	43·04	0·024
	3·83	49·54	106·5	1·91	0·06	0·21	47·68	1·86	51·24	0·025
				39·3% Glycol, D = 66·8.						
5·27	6·98	56·76	117·8	5·65	0·08	0·10	55·51	1·23	62·31	0·145
				51·2% Glycol, D = 62·8.						
4·61	5·52	24·40	28·40	4·92	0·06	0·04	23·87	0·54	29·28	0·139
	6·06	43·92	52·06	4·96	0·06	0·07	42·88	1·04	48·81	0·118
				63·1% Glycol, D = 59·0.						
3·98	4·91	24·40	28·40	4·27	0·05	0·04	23·81	0·59	28·63	0·105
				15·0% Dioxan, D = 63·3.						
5·16	6·52	30·96	35·22	5·34	0·10	0·08	29·89	1·07	36·21	0·092
	7·07	51·60	57·76	5·43	0·11	0·14	50·07	1·53	56·89	0·100
				22·5% Dioxan, D = 55·5.						
4·03	6·05	50·41	56·49	4·25	0·10	0·17	48·71	1·70	54·49	0·061
				31·7% Glycerol, D = 69·5.						
7·09	8·33	30·96	34·37	7·46	0·10	0·05	30·18	0·77	38·37	0·194
	8·90	51·60	57·76	7·57	0·10	0·09	50·37	1·23	59·08	0·187
				42·3% Glycerol, D = 66·4.						
6·75	8·01	29·27	33·81	7·10	0·10	0·05	28·46	0·81	36·32	0·159
	8·60	51·60	57·76	7·27	0·10	0·09	50·39	1·23	58·80	0·173

seen that the different solvents give characteristic slopes, although there is little to choose between methanol, ethanol, and acetone. The average value of K in water (0·23) is comparable with that (0·19) obtained by an e.m.f. method (MacDougall and Peterson, *J. Physical Chem.*, 1947, **51**, 1346).

The variation of log K with D predicted by Bjerrum's equation (*Kgl. Danske Vidensk. Selskab.*, 1926, **7**, No. 9) is the broken line in Fig. 1. Its failure to coincide with any of the experimental lines may not be due to any error in the equation, which is based essentially on the forces of association being electrostatic in nature. Use of the value of K obtained with aqueous solutions leads to 0·91 Å as the mean distance of approach of the two ions as calculated from Bjerrum's equation, whereas the radius of the unhydrated silver ion is itself 1·26 Å (Harned and Owen, *loc. cit.*), which suggests that the association may well be founded on chelation forces.

James (*loc. cit.*, 1950) has shown that Bjerrum's equation accounts reasonably well for the variations in the dissociation constant of lanthanum ferricyanide when the organic solvent mixed with water is dioxan, glycol, acetone, or ethanol, but that this is not so with copper

FIG. 1.

Dissociation constants of silver acetate.

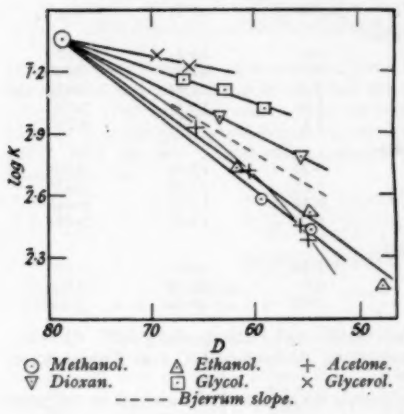
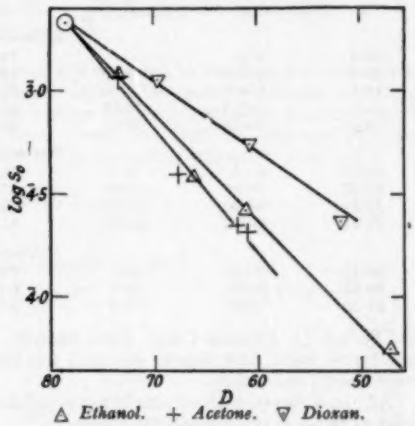


FIG. 2.

Silver acetate solubilities.



sulphate, zinc sulphate, or zinc malonate (although with the last salt it is again probable that the associating forces are of a chelating character so that Bjerrum's treatment is scarcely valid). With zinc and copper sulphates it is possible that ion solvation is an important factor in influencing the rate of change of K with D, and that this varies with the nature of the solvent. It is worth notice in this respect that the rate of change with different solvents is in the same order with these sulphates as in the case of silver acetate, *i.e.*, ethanol > acetone > dioxan > glycol (over the same range of D). Unfortunately it is difficult to reconcile this view of varying ion solvation with the behaviour of lanthanum ferricyanide where no really large differences appear on change of the solvent. In addition, both with this salt and with the zinc and copper salts, all of which were studied by the conductivity method, the Walden–Stokes product, $\Lambda^{\circ}\eta$, remains approximately constant when the proportion of organic solvent is increased, indicating that the effective ionic radii are not changing markedly. This suggests that water molecules are being replaced in the sphere of ion solvation by organic solvent molecules. This, of course, is the basic idea of Debye's "salting effect" (Debye and McAulay, *Physikal. Z.*, 1925, **26**, 22), namely, that in a solution of mixed polar molecules the ions tend to sort out the dipoles, the more polar molecules tending to concentrate round the ions. There is, however, lack of agreement between this theory and experimental evidence, as pointed out by Scatchard (*J. Chem. Physics*, 1941, **9**, 34) and others, probably owing to neglect of the discrete structure of the solvent.

The lower solubility shown by salts as the dielectric constant is lowered is analogous to the

fall in the dissociation constant. This has been investigated by numerous workers, many of whom have compared their results with the relation

$$\ln (S_1/S_2) = (z_1 z_2 e^2/2rkT)(1/D_2 - 1/D_1)$$

where S_1 and S_2 are the solubilities at dielectric constants D_1 and D_2, and r is the mean radius of the electrolyte ions of valencies z_1 and z_2. This expression was obtained by both Born (*Z. Physik*, 1920, **1**, 45) and Scatchard (*Chem. Reviews*, 1927, **3**, 383). In general, it gives values of r which are too small. Since results have been published for the solubility of silver acetate in several of the mixed solvents discussed in this paper, it is worth seeing if corrections for both ion association and interionic effects can reconcile the theory with the results. When allowance is made for undissociated silver acetate and for the ionic strengths of the solutions, the above expression becomes

$$\ln (S_1^\circ/S_2^\circ) = (e^2/rkT)(1/D_2 - 1/D_1)$$

where S_1° and S_2° are the activity solubility product calculated by an expression similar to that used for silver bromate. The calculations are summarised in Table III [the data of MacDougall

TABLE III.

Silver acetate solubilities (all concns., $\times 10^{-3}$).

S	K	Organic solvent, %	D	[AgOAc]	10^3I	$-\log S_a$
			Ethanol–water.			
66·3	0·23	—	78·5	9·4	56·9	2·671
50·6	0·155	9·00	73·4	7·7	42·9	2·915
29·4	0·068	25·06	64·1	5·5	23·9	3·418
24·9	0·053	30·05	61·1	5·0	19·9	3·577
12·4	0·019	50·14	48·6	3·1	9·3	4·245
			Acetone–water.			
49·90	0·15	9·27	73·4	7·86	42·04	2·932
32·37	0·097	18·83	67·7	5·15	27·22	3·400
21·40	0·060	28·25	62·0	3·74	17·66	3·648
21·31	0·056	30·02	61·0	3·74	17·57	3·676
			Dioxan–water.			
50·32	0·135	10·0	69·7	8·37	41·97	2·947
36·38	0·083	20·0	60·8	6·65	29·73	3·261
24·52	0·051	30·0	51·9	4·63	19·89	3·626

and Batsch (*J. Physical Chem.*, 1936, **40**, 649), MacDougall and Larson (*ibid.*, 1937, **41**, 417), and Davis, Ricci, and Sauter (*loc. cit.*) for ethanol–water, acetone–water, and dioxan–water respectively, were used].

As Fig. 2 shows, each solvent again gives characteristic slopes, but these are not in the same order as those of the dissociation constants.

Wynne-Jones (*Proc. Roy. Soc.*, 1933, *A*, **140**, 440) has expressed the relations between K and D in a form similar to the above solubility expression for the dissociation of acids, which for the present purpose may be written :

$$\ln (K_1/K_2) = (z_1 z_2 e^2)/(rkT)(1/D_2 - 1/D_1)$$

Although there is no specific value of r which will satisfy this equation for all three cases discussed with regard to solubilities, we might expect to find that the values of r obtained by the above two expressions are approximately equal. Calculation gives the following figures :

	Acetone–water	Ethanol–water	Dioxan–water
Dissociation constants : r(Å)	1·42	1·43	3·10
Solubilities : r(Å)	0·85	1·01	1·63
Ratios	1·17	1·4	1·9

The fluctuating ratios and their departure from unity can only suggest that there are deficiencies in both of the equations used or that, as discussed earlier, ion–solvent (or perhaps ion pair–solvent) interactions are of major importance. It is thus worth comparing an independent calculation of r with the above figures. By using Stokes' law, the limiting mobility of the acetate ion, which is 40·9 (Harned and Owen, *loc. cit.*, p. 172) gives the acetate radius as 2·2 Å, and the limiting mobility of the silver ion (61·92) gives that of silver as 1·5 Å. The average, 1·8 Å, is half to twice the tabulated figures, a range which is not supported by the conductivity evidence discussed earlier on.

Broadly speaking, the solvents may be classified into (*a*) ethanol and acetone, which markedly reduce the solubilities and the dissociation constants, and (*b*) dioxan and glycol which have less effect; these generalisations apply to the zinc, copper, and silver salts. The wider range of solvents used in the study of silver acetate further indicates that longer molecules and those with more hydroxyl groups have the smaller influence. It is of significance in this respect to find that sucrose actually increases the (aqueous) dissociation constants of several organic acids (Davey and Dippy, *J.*, 1944, 411; Kolthoff, *Rec. Trav. chim.*, 1929, **48**, 220) although sucrose solutions have lower dielectric constants than that of water.

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605. *The Influence of Mixed Solvents on the Solubilities of Salts.*

By C. B. MONK.

The solubilities of several sparingly soluble iodates have been measured in various mixed solvents. The results indicate that the chemical character of the solvent is of major importance in influencing the decrease in solubility with decreasing dielectic constant of the solution.

IN general, the solubility of a salt at a given temperature is related to the dielectric constant of the solvent, but there is no doubt that the chemical nature of the solvent also has a decided influence. For mixed solvents one of the best illustrations is provided by silver bromate, which has received detailed consideration by Owen (*J. Amer. Chem. Soc.*, 1933, **55**, 1922) and Neuman (*ibid.*, 1934, **28**, 56). Using the expression given in the preceding paper, we may write, for these solutions:

$$\log S_0 = \log [Ag^+][BrO_3^-] - F'(I)$$

TABLE I.

Silver bromate solubilities (Concns., $\times 10^{-3}$).

Organic solvent, %	Methanol[a] S	D	$-\log S_0$	Ethanol[a] S	D	$-\log S_0$	*n*-Propanol[a] S	D	$-\log S_0$
0	8·12	78·5	4·263	—	—	—	—	—	—
10	5·51	74·1	4·592	5·53	72·8	4·592	5·80	71·8	4·553
20	3·79	69·2	4·912	3·86	67·0	4·900	4·36	64·9	4·803
30	2·65	64·3	5·220	2·78	61·1	5·184	3·31	57·7	5·046
40	1·82	59·6	5·541	1·97	55·0	5·483	2·41	50·3	5·326
50	1·24	54·9	5·871	1·36	49·0	5·805	1·63	43·0	5·671
60	0·83	50·1	6·216	—	—	—	—	—	—
70	—	—	—	—	—	—	—	—	—
80	—	—	—	—	—	—	—	—	—

Organic solvent, %	Mannitol[a] S	D	$-\log S_0$	Organic solvent, %	*iso*Propanol[b] S	D	$-\log S_0$	Organic solvent, %	Dioxan[a] S	D	$-\log S_0$
5	8·24	77·8	4·251	11·12	5·29	70·6	4·631	10	6·24	69·7	4·496
10	8·38	77·1	4·238	22·90	3·60	62·4	4·966	20	4·76	60·8	4·739
15	8·51	76·3	4·227	31·16	2·81	56·0	5·185				
				39·77	2·10	49·7	5·442				

Organic solvent, %	Acetone[a] S	D	$-\log S_0$	Ethylene glycol[a] S	D	$-\log S_0$	Glycerol[a] S	D	$-\log S_0$
0	—	—	—	—	—	—	—	—	—
10	5·92	73·0	4·534	7·26	75·6	4·361	7·80	75·5	4·300
20	4·29	67·0	4·812	6·50	72·8	4·456	7·49	72·9	4·338
30	3·00	61·0	5·121	5·85	69·8	4·549	7·15	70·0	4·382
40	2·03	54·6	5·459	5·26	66·6	4·643	6·84	67·1	4·425
50	—	—	—	4·70	63·2	4·743	6·48	64·0	4·476
60	—	—	—	—	—	—	6·08	60·0	4·539
70	—	—	—	3·61	54·7	4·981	5·59	55·6	4·620
80	—	—	—	—	—	—	4·94	50·6	4·738

[a] Owen, *loc. cit.* [b] Neuman, *loc. cit.* [c] Present work.

Strictly, allowance should be made for undissociated silver bromate (see preceding paper), but little error is introduced by not doing so, and the figures given in Table I are thereby obtained. The characteristic variations in the solubilities as the type of solvent is changed is shown clearly on plotting $-\log S_0$ against D (see Fig. 1).

As an extension of this work, the solubilities of calcium, barium, and lanthanum iodates have been determined in some mixed solvents. These salts were chosen since they are reasonably strong electrolytes; the dissociation constant of $Ca(IO_3)^+$ in water is 0·13 (Wise and Davies, *J.*, 1938, 273), that of $Ba(IO_3)^+$ is 0·09 (Macdougall and Davies, *J.*, 1935, 1416), and while that of $La(IO_3)^{2+}$ is unknown, the dissociation is probably quite large as the corresponding chloride appears to be fully ionised (James and Monk, *Trans. Faraday Soc.*, 1950, **46**, 1041). Accordingly no serious errors are involved in regarding these three iodates as being completely dissociated.

Experimental.

Calcium iodate crystals were prepared by Wise and Davies's method (*loc. cit.*), and barium iodate by allowing dilute solutions of potassium iodate and of barium chloride to drip slowly into hot water. Crystals of lanthanum iodate were formed by LaMer and Goldman's method (*J. Amer. Chem. Soc.*, 1929, **51**, 2632) by using lanthanum chloride prepared from "Spec-pure" lanthanum oxide; these crystals were too fine for use, but larger ones of suitable size were obtained by dissolution in water followed by evaporation.

Fig. 1.

Silver bromate.

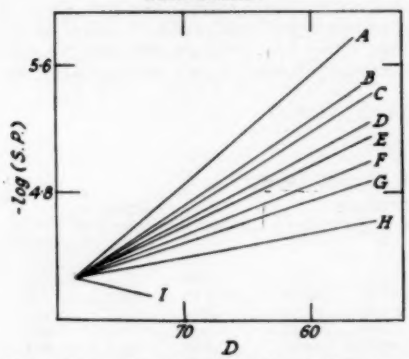
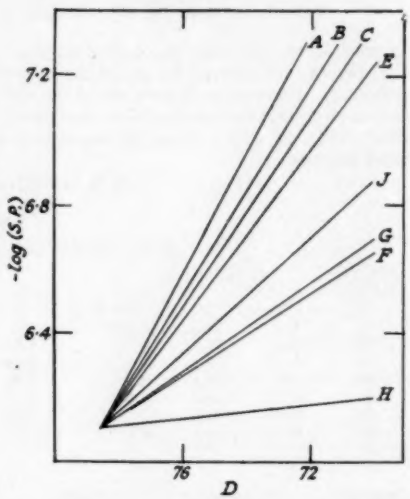


Fig. 2.

Calcium iodate.



Key to Figs. *A* methanol, *B* ethanol, *C* acetone, *D* *iso*propanol, *E* *n*-propanol, *F* glycol, *G* dioxan, *H* glycerol, *I* mannitol, and *J* ethyl acetate.

The organic solvents used were of laboratory grade, except in the cases of acetone and dioxan (AnalaR). Ethyl acetate was purified by shaking it with aqueous sodium carbonate, followed by fractional distillation.

The types of saturators used, and the experimental procedure of determining the solubilities (at 25° ± 0·03°) have been described previously (Monk, *Trans. Faraday Soc.*, 1951, **47**, 285). The saturated solutions containing dioxan were corrected for peroxides by blank titrations. Each solvent mixture was made by dilution of a stock solution, the density of which was determined. From these densities, the composition of each solution was calculated from available data, *viz.*, Owen, *loc. cit.* (methanol), Int. Crit. Tables, Vol. III, pp. 114, 117 (ethanol, *n*-propanol, ethyl acetate), Squibb, *J. Amer. Chem. Soc.*, 1895, **17**, 187 (acetone), Knight, Massi, and Roesel, *ibid.*, 1946, **68**, 641 (glycol), Davis, Ricci, and Sauter, *ibid.*, 1939, **61**, 3274 (dioxan), and Bosart and Snoddy, *J. Ind. Eng. Chem.*, 1927, **19**, 506 (glycerol). Dielectric constants were obtained by interpolation from the data given by Harned and Owen ("The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1943, p. 118) except in the case of ethyl acetate (Albright and Williams, *Trans. Faraday Soc.*, 1937, **33**, 247).

The results are recorded in Table II, where the concentrations are given in millimols. per l. D represents the dielectric constants of the solvents, and {S.P.} the activity solubility products; these have been calculated from the equations

$$\log \{S.P.\} = \log [M^{2+}][IO_3^-]^2 - 3F'(I) \quad (M = Ca, Ba)$$

and

$$\log \{S.P.\} = \log [La^{3+}][IO_3^-]^3 - 6F'(I)$$

Discussion.

The results given in Table II are plotted as $-\log \{S.P\}$ against D in Figs. 2, 3, and 4. These plots are more linear than when plotted against $1/D$ (Owen, *loc. cit.*). Comparison of Figs. 1,

Fig. 3.

Barium iodate.

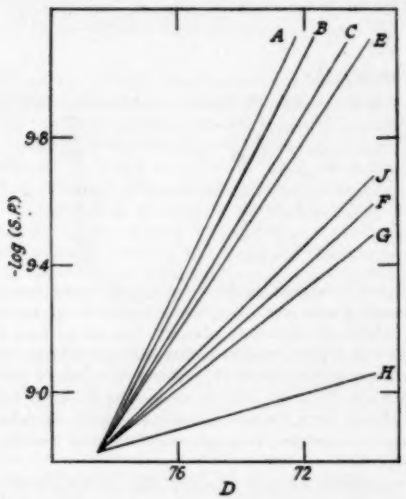
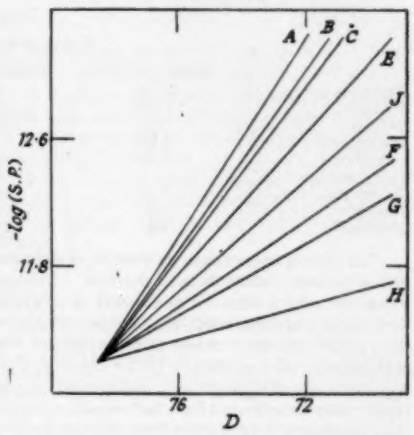


Fig. 4.

Lanthanum iodate.



2, 3, and 4 shows that, apart from minor deviations, the slopes lie in the same order with each salt. In the previous paper, reference was made to the Born–Scatchard solubility expression.

Table II.

Calcium, barium, and lanthanum iodate solubilities.

Solvent.	%.	D.	$Ca(10_3)_2$, $\times 10^{-3}$.	$-\log \{S.P.\}$.	$Ba(10_3)_2$, $\times 10^{-4}$.	$-\log \{S.P.\}$.	$La(10_3)_3$, $\times 10^{-4}$.	$-\log \{S.P.\}$.
Water	100	78·5	7·84	6·100	8·12	8·809	8·83	11·186
Methanol	4·72	76·5	4·88	6·501	5·71	9·252	5·78	11·867
	9·53	74·3	4·02	6·900	4·05	9·686	3·99	12·469
	14·43	72·1	2·94	7·280	2·84	10·136	2·70	13·109
Ethanol	3·82	76·4	5·83	6·463	5·80	9·232	5·95	11·821
	7·67	74·1	4·33	6·818	4·18	9·644	4·20	12·387
	11·59	72·1	3·23	7·170	3·02	10·058	2·89	12·999
Acetone	4·09	76·3	5·91	6·446	5·99	9·195	6·01	11·805
	8·25	73·9	4·46	6·787	4·46	9·566	4·28	12·356
	12·46	71·7	3·32	7·145	3·27	9·959	3·01	13·065
n-Propanol	4·16	75·8	5·72	6·482	5·78	9·238	5·92	11·833
	8·40	72·9	4·20	6·862	4·13	9·664	4·08	12·441
	12·71	70·0	3·07	7·243	2·94	10·096	2·84	13·039
Ethyl acetate	3·8	75·6	6·26	6·378	6·42	9·108	6·55	11·673
	6·1	73·8	5·50	6·541	5·59	9·284	5·59	11·936
Dioxan	2·2	76·6	7·04	6·239	7·15	8·972	7·69	11·416
	4·7	74·4	6·26	6·388	6·04	9·145	6·63	11·663
	9·4	70·2	4·93	6·694	4·72	9·504	4·88	12·175
	10·0	69·7	—	—	4·74	9·500	—	—
Glycol	5·62	76·9	7·16	6·216	7·18	8·966	7·50	11·452
	11·24	75·3	6·60	6·321	6·40	9·113	6·69	11·641
	16·85	73·7	6·12	6·420	5·73	9·253	5·91	11·847
Glycerol	6·31	76·6	7·75	6·118	7·81	8·859	8·22	11·316
	12·44	74·8	7·70	6·147	7·52	8·914	7·89	11·387
	18·43	73·3	7·70	6·161	7·28	8·958	7·61	11·456

For the two types of salts under discussion the appropriate expressions are, for calcium and barium iodates:

$$\ln (\{S.P._1\}/\{S.P._2\}) = (3e^2)/(rkT)(1/D_2 - 1/D_1)$$

and for lanthanum iodate:

$$\ln \{S.P._1\}/\{S.P._2\} = (6e^2)/(rkT)(1/D_2 - 1/D_1)$$

The resulting values of r for these three salts and for silver bromate are given in Table III.

TABLE III.

Calculated values of r (Å).

	Silver bromate	Calcium iodate	Barium iodate	Lanthanum iodate
Methanol	0·78	0·68	0·66	0·87
Ethanol	0·98	0·82	0·71	0·90
Acetone	1·05	0·90	0·82	1·03
*iso*Propanol	1·23	—	—	—
n-Propanol	1·35	1·0	0·89	1·2
Ethyl acetate	—	1·4	1·4	1·5
Glycol	1·63	2·1	1·2	1·9
Dioxan	2·0	2·2	1·7	2·3
Glycerol	3·5	14·0	6·0	5·0

The figures being taken as a whole, it is evident that r is characteristic of the organic constituent of the solvent rather than of the salt. The outstanding exception is calcium iodate in glycerol solutions, which may be the result of a specific cation–glycerol interaction. So far as minor deviations are concerned, the slightly smaller values of r with barium iodate may be related to the smaller effective radius of the hydrated barium ion as compared with those of calcium and lanthanum. A comparison of the slopes of the curves in the Figs. with those for the dissociation constants of silver acetate in the preceding paper shows some general features, namely, that in both instances glycerol has the less effect, and the group acetone, ethanol, and methanol has the most influence, whilst glycol and dioxan are intermediate.

It would appear then that further theoretical treatment lies in a consideration of the solvent properties. As the dielectric constant is varied the composition of the solvent alters also, and this is attended by specific energy changes. Accordingly, the organic solvent–water, organic solvent–ion, and water–ion interactions are all dependent on the proportions and nature of the organic constituent.

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606. *The Fluorination of Some Volatile Chlorides with Ammonium Fluoride.*

By C. J. WILKINS.

Halogen exchange occurs when ammonium fluoride is heated with certain volatile chlorides. In some cases useful yields of monofluoride chlorides may be obtained without special control of the conditions.

SEVERAL applications of ammonium fluoride for the fluorination of covalent halides have been reported, but their nature suggests that a more complete survey of its potentialities in this field is required. It is, for example, one of the few reagents suitable for halogen-exchange fluorination of arsenic halides under mild conditions (MacIvor, *Chem. News*, 1874, **30**, 169; 1875, **32**, 258; Long, Emeléus, and Briscoe, *J.*, 1946, 1123). Moreover, the ammonium fluoride–ammonium chloride couple stands high in a table recently drawn up by Woyski (*J. Amer. Chem. Soc.*, 1950, **72**, 919) in which fluoride–chloride couples are listed in order of increasing free energies of fluoride–chloride exchange processes, so that equilibrium conditions can be expected to be favourable to occurrence of halogen exchange between ammonium fluoride and most covalent chlorides.

In the present experiments halogen exchange was observed between ammonium fluoride and chlorides of silicon, phosphorus, arsenic, and antimony, and of the halides examined *NN*-dichloroethylamine alone failed to react. From a practical viewpoint the reactions with chlorides of silicon and phosphorus which were examined are notable for the ease with which the monofluoride chlorides listed below may be obtained even without recourse to any special control of reaction conditions :

Chloride	$SiCl_4$	$SiEt_2Cl_2$	PCl_3	$POCl_3$
Fluoride chlorides isolated	$SiCl_3F$	$SiEt_2ClF$	PCl_2F	$POCl_2F$
				$POClF_2$

Except for diethylchlorofluorosilane, not previously described, such products have been obtained by Booth and his co-workers (*J. Amer. Chem. Soc.*, 1932—49) by the use of antimony trifluoride only under rather elaborately controlled conditions. A similar predominance of monofluorinated intermediates has been observed in these fluorinations with antimony trifluoride, and has been ascribed by Booth and Bozarth (*ibid.*, 1939, **61**, 2927) to the progressively more rapid fluorination of the successive intermediates under the same experimental conditions.

Fluorination of arsenic trichloride failed to yield the fluoride chlorides, which are as yet unknown. In similar experiments with methyldichlorostibine and dimethylchlorostibine the sole volatile product was trimethylstibine, obtained in almost quantitative yield, suggesting complete disproportionation of the methylfluorostibines.

Experimental.

The chlorides were heated under reflux with dry, finely crystalline, AnalaR-quality ammonium fluoride, and the gaseous or more volatile fluorinated material passing through the condenser was retained in a cold trap. The ammonium fluoride used was found by analysis to contain not more than 2% of the hydrogen fluoride. The product from the cold trap was fractionally distilled through an 18″ column packed with glass helices and having a water-cooled or low-temperature head, as appropriate. Where refluxing temperatures were low, reactions became very slow after an initial period of more rapid fluorination but such reactions required little attention. Similar proportions of the various products were obtained from the initial and later stages of these reactions. Low-boiling fluorides were purified and identified tensimetrically in a vacuum system.

Fluorination of Silicon Tetrachloride, Phosphorus Trichloride, and Phosphoryl Trichloride.—Experimental data are summarised in the table.

Reactants (g.)	Reaction time (hrs.)	Product	Yields (g.)	B. p./mm.	Cl, % Found	Cl, % Calc.
$SiCl_4$, 170	100	$SiCl_3F$	5	12·0–12·4°/758	—	—
NH_4F, 75		SiF_4	8	—	—	—
PCl_3, 200	100	PCl_2F	3·5	13·4—13·9°/757	58·1	58·7
NH_4F, 68		PF_3	9	—	—	—
$POCl_3$, 154	8	$POCl_2F$	16	52·0—52·2°/745	51·5	51·8
NH_4F, 74		$POClF_2$	7	2·5—2·9°/745	28·5	29·6
		POF_3	39	—	—	—

Boiling points and vapour pressure curves of the fluoride chlorides agreed closely with those reported by Booth (*loc. cit.*). For chloride analyses the compounds were redistilled, weighed, and absorbed in alkali, with standard vacuum technique, and the chloride was determined gravimetrically.

Fluorination of Diethyldichlorosilane.—The reaction was carried out in a flask fitted with fractionating column, and bearing a side-arm through which successive small quantities of ammonium fluoride could be introduced as reaction proceeded. In a typical fluorination 0·35 g.-mol. of diethyldichlorosilane (b. p. 128—130°) was carefully heated with ammonium fluoride (4 g.) and the reflux ratio adjusted so as to keep the distillation temperature at 95—105°. As the reaction slackened a further small quantity (2—3 g.) of ammonium fluoride was added through the side-arm, and the process repeated until a total of 0·65 g.-mol. of ammonium fluoride had been added. Addition of xylene towards the end of the operation rendered distillation of fluorinated material more complete, and also served to keep the reaction mixture mobile. Redistillation of the product gave about 30 g. of diethyldifluorosilane, b. p. 62·0—62·5°/760 mm., and 4 g. of *diethylchlorofluorosilane*, b. p. 96—97°/758 mm. For analysis the compounds were absorbed in excess of 0·7*N*.-alkali, the solutions were boiled to ensure complete hydrolysis, and excess of alkali was back-titrated. The chlorine content of the fluoride chloride was determined gravimetrically and by Mohr's titration method [Found : (*a*) Fraction, b. p. 62·0—62·5° : 0·0158 equiv. of acid/g. Calc. for $C_4H_{10}F_2Si$: 0·0161. (*b*) Fraction, b. p. 96—97° : 0·0140 equiv. of acid/g.; Cl, 26·0. $C_4H_{10}ClFSi$ requires 0·0142 equiv./g.; Cl, 25·3%].

Fluorination of Arsenic Trichloride.—This was carried out by a procedure similar to that for the fluorination of diethyldichlorosilane. The only product was arsenic trifluoride, b. p. 60—61°, with no indication of the presence of material of intermediate volatility.

Reactions of Ammonium Fluoride with Methyldichlorostibine and Dimethylchlorostibine.—These reactions were carried out under nitrogen to avoid complications from oxidation. Both stibines reacted readily at 90°. Volatile products from both reactions were found from measurement of vapour pressures and vapour densities to consist of trimethylstibine only. As a typical yield, 342 c.c. were obtained from 4·5 g. of dimethylchlorostibine (Found : *M*, 167·3. Calc. for C_3H_9Sb : *M*, 166·8).

The author is indebted to Professor H. J. Emeléus, F.R.S., for his interest, and acknowledges a research grant from the University of New Zealand.

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607. *A New Sterol from a Strain of* Aspergillus niger.

By D. H. R. BARTON and T. BRUUN.

A new tetraethenoid sterol, isolated from the non-saponifiable matter of a strain of *Aspergillus niger*, has been proved to be 14-dehydroergosterol. It occurs as a minor component in admixture with ergosterol.

THE mould *Aspergillus niger* is of industrial importance for the manufacture of citric acid. A by-product of this process is ergosterol, isolated from the mycelium by extraction with alcohol and hydrolysis. Many strains of this mould are known, only a few of which are useful commercially. One such strain, under investigation in the laboratories of Messrs. J. and E. Sturge Ltd., Birmingham, was found to furnish an ergosterol which was *more* lævorotatory than pure ergosterol (see Barton and Cox, *J.*, 1948, 783, 1357). Other strains of *A. niger*, investigated in these laboratories and equally satisfactory for the production of citric acid, have always furnished essentially pure ergosterol. The existence of this anomaly was first brought to our attention by Dr. E. R. S. Winter, Director of Research at Messrs. J. and E. Sturge Ltd., who kindly advised us during the initial stages of the investigation and provided us with an adequate supply of raw material.

The main component of the anomalously rotating sterol was the expected ergosterol, present to an extent of 82% as judged by the absorption spectrum. That the strongly lævorotatory contaminant was possibly a sterol was shown by its digitonin precipitability. It was separated from ergosterol by prolonged recrystallisation of the mixed benzoates—care was needed because even traces of acids, such as the hydrogen chloride present in aged batches of chloroform, were sufficient to destroy the strongly lævorotatory benzoate (see Experimental). In this way a pure benzoate, $C_{35}H_{46}O_2$, m. p. 208—212°, $[\alpha]_D$ −274° (in chloroform), −260° (in carbon tetrachloride), was finally obtained. This showed a characteristic absorption band (see figure) at 319 mμ. ($\varepsilon_{max.}$ 16,000 in ethanol). It was shown to be 14-dehydroergosteryl benzoate (I; R = Bz) by the reactions summarised in the sequel on p. 2730.

On catalytic hydrogenation with a platinum catalyst in acetic acid solution the benzoate afforded, in almost quantitative yield, " α "-ergostenyl hexahydrobenzoate (II; R = C_6H_{11}·CO), the constitution • of which was confirmed (*a*) by hydrolysis to " α "-ergostenol and hexahydrobenzoic acid and (*b*) by its preparation by the similar hydrogenations of " α "-ergostenyl benzoate (II; R = Bz) and of ergosteryl benzoate (III). This established the nature of the carbon skeleton and indicated the presence of at least one double bond at position 7(8), 8(9), and/or 8(14).

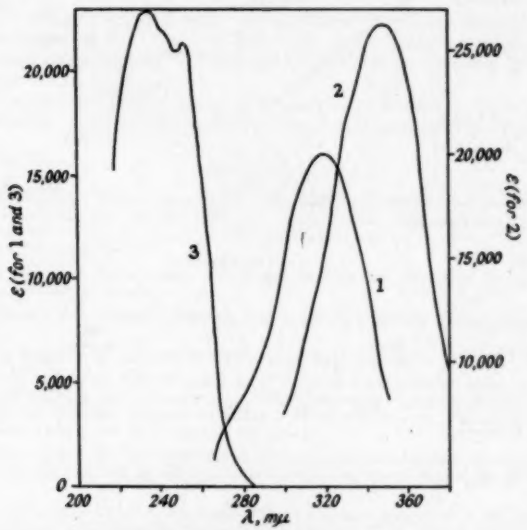
With maleic anhydride in refluxing benzene—conditions under which ergosteryl benzoate itself does not react (Inhoffen, *Annalen*, 1934, **508**, 81)—the new benzoate gave a beautifully crystalline adduct (IV), which showed no butadienyl absorption in the ultra-violet region. The position of attachment of the maleic anhydride residue was proved by catalytic hydro-

• It is a curious discrepancy in the literature that our " α "-ergostenyl hexahydrobenzoate appears to be identical with a substance described as ' " α "-ergostenyl benzoate ' by Wieland, Rath, and Hesse (*Annalen*, 1941, **548**, 34). The latter was prepared by methods comparable to those employed here for the preparation of the hexahydrobenzoate. We have always found that α-ergostenyl benzoate melts at 116° and has $[\alpha]_D$ ±0° (in chloroform). It is possible that the ' " α "-ergostenyl benzoate ' of Wieland, Rath, and Hesse is a higher-melting form but against this possibility stand (*a*) the methods of preparation and (*b*) the fact that there was no depression in m. p. on admixture of our " α "-ergostenyl hexahydrobenzoate with the ' " α "-ergostenyl benzoate ' of Wieland, Rath, and Hesse. We are greatly indebted to Professor H. Wieland, for the latter observation.

genation to give the monoethenoid dihydroergosteryl B_3 hexahydrobenzoate–maleic anhydride adduct (V). An authentic specimen of (V) was prepared by reaction of ergosteryl B_3 benzoate (VI; R = Bz) (see Barton, *J.*, 1946, 513; Barton and Brooks, *J.*, 1951, 277) with maleic anhydride to give the adduct (VII), followed by catalytic hydrogenation. These experiments indicated the existence of double bonds at positions 7(8) and 14(15) in the adduct precursor.

The presence of an ethylenic linkage at the 22(23)-position in the side chain was proved by ozonolysis of the benzoate–maleic anhydride adduct. This afforded the same 2 : 3-dimethylbutanal, characterised as the lævorotatory semicarbazone, as is obtained in the same way from ergosterol and its derivatives retaining the 22(23)-ethylenic linkage.

It was mentioned above that the new strongly lævorotatory benzoate was characterised by an absorption band at 319 mμ. This was interpreted to imply the presence of three double bonds in conjugation, two being present in one ring (Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., 3rd Edn., p. 188; the calculated $\lambda_{max.}$ for 14-dehydroergosterol is 323 mμ, in excellent agreement with that found by experiment).

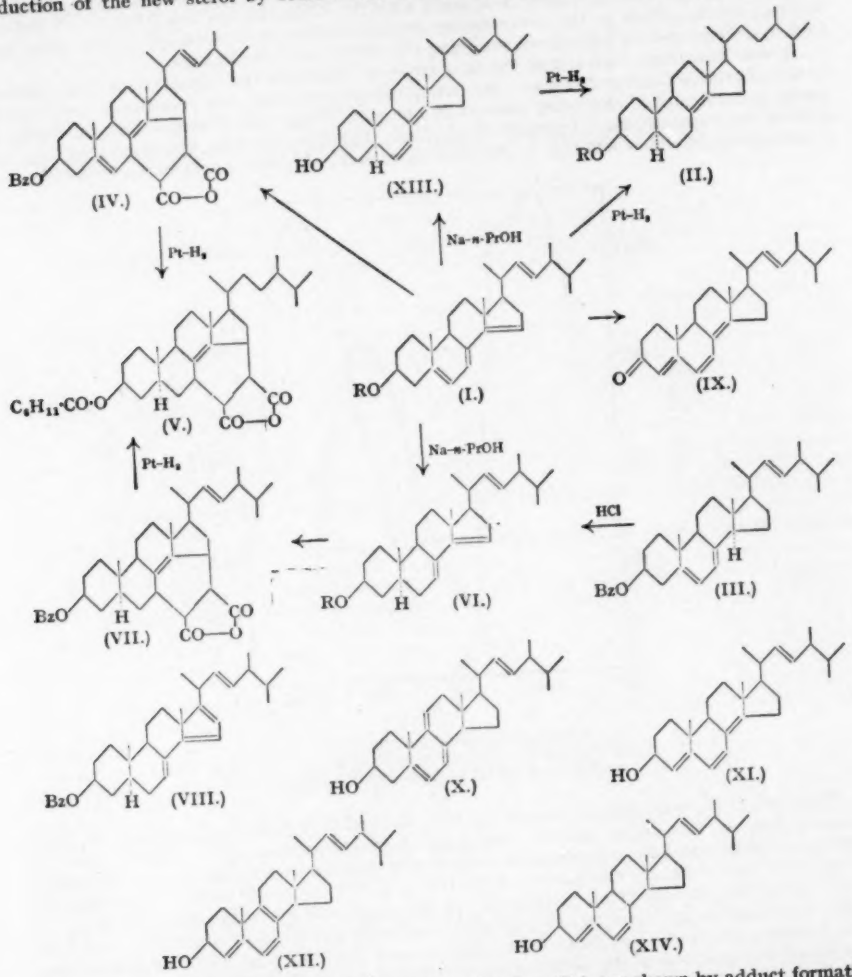


1. 14-*Dehydroergosteryl benzoate.*
2. *Ergosta*-4 : 6 : 8(14) : 22-*tetraen*-3-*one.*
3. *Ergosta*-6 : 8(14) : 22-*trien*-3β-*yl benzoate.*

There are, then, two possible formulæ (I; R = Bz) and (VIII), for the benzoate. A choice between them was made as follows. Although alkaline hydrolysis of the benzoate led to destruction of material by resinification, reductive hydrolysis by lithium aluminium hydride afforded without difficulty the parent sterol (I; R = H), m. p. 198—201° (decomp.), $[\alpha]_D$ −396° (in carbon tetrachloride), characterised as the acetate and by reconversion into the benzoate. Oxidation of the sterol by the Oppenauer method, followed by careful chromatography, gave ergosta-4 : 6 : 8(14) : 22-tetraen-3-one (IX), m. p. 114—115°, $[\alpha]_D$ +590° (in chloroform). The absorption spectrum of this ketone [$\lambda_{max.}$ 348 mμ; $\varepsilon_{max.}$ 26,500 in ethanol (see Fig.)] showed that there were three double bonds in conjugation (in three different rings) with the keto-group (cf. Fieser and Fieser, *op. cit.*, p. 192). In agreement, the corresponding 2 : 4-dinitrophenylhydrazone had $\lambda_{max.}$ 427 mμ, $\varepsilon_{max.}$ 41,000 in chloroform (cf. Braude and Jones, *J.*, 1945, 498). This excludes (VIII) from further consideration, for a conjugated ketone could not have been obtained on Oppenauer oxidation of the corresponding sterol.

It is a possible criticism of this proof of structure that rearrangement of the three conjugated ethylenic linkages might occur during the formation of the maleic anhydride adduct (IV), although such is not the case with ordinary dehydroergosterol (X) (Honigmann, *Annalen*,

1934, **508**, 89). If for the moment this point of view is accepted, there would then be three possible formulæ (I; R = H), (XI), and (XII) which would explain the formation of (IX) on Oppenauer oxidation. Of these, (XI) is possibly excluded on spectral grounds as it should show $\lambda_{max.}$ about 279 mμ in ethanol (Fieser and Fieser, *op. cit.*, p. 188) rather than $\lambda_{max.}$ 323 mμ (see above). Decisive chemical evidence for the exclusion of (XI) and (XII) was obtained by reduction of the new sterol by sodium and boiling *n*-propanol. After benzoylation of the



product, the presence of ergosteryl B_3 benzoate (VI; R = Bz) was shown by adduct formation with maleic anhydride. Careful chromatography of the portion of the benzoate which did not react with maleic anhydride afforded one fraction which, from its absorption spectrum, contained about 50% of ergosteryl benzoate. The main product of reduction was, however, a new conjugated-dienyl benzoate, m. p. 129—130°, $[\alpha]_D$ −104° (in chloroform), $\lambda_{max.}$ 252 mμ, $\varepsilon_{max.}$ 23,000 in ethanol (see Fig.), which had the formula $C_{35}H_{48}O_2$ and was, therefore, a triene. It was further characterised by hydrolysis to the parent sterol and by conversion of the latter into the acetate. As justified in detail below, this triene must be ergosta-6 : 8(14) : 22-trien-

3β-ol (XIII). The formation of this compound, and especially of ergosterol B_2 (VI; R = H) by reduction under conditions where double-bond migrations, outside the extent of the original conjugated triene system, are excluded, provides final proof for the correctness of the formula (I; R = H) for the new sterol from *A. niger*. Incidentally the formation of ergosterol B_2 in this way also proves that the configuration about the 22(23)-ethylenic linkage is the same (*trans*) (Turnbull, Whiffen, and Wilson, *Chem. and Ind.*, 1950, 626; R. Norman Jones, *J. Amer. Chem. Soc.*, 1950, **72**, 5322) as in ergosterol.

The formula (XIII) assigned to the new conjugated diene was deduced from the following evidence. The two conjugated double bonds must be in two different rings because of the absorption spectrum. Catalytic hydrogenation of the acetate afforded "α"-ergostenyl acetate (II; R = Ac) in excellent yield. This excludes formula (XIV), which in any case is known (Güntzel, *Ber.*, 1939, **72**, 1317), in favour of (XIII). In confirmation, isomerisation of the benzoate by hydrogen chloride in chloroform gave ergosteryl B_2 benzoate, characterised as the maleic anhydride adduct. The formation of (XIII) by reduction is an excellent example of 1 : 6-addition.

Formula (XIII) was previously assigned, on the basis, mainly, of exclusion evidence (Barton, *J.*, 1946, 512), to ergosterol B_2. The constants that we now record for (XIII) are in moderate agreement only with those reported for ergosterol B_2 (Windaus, Dithmar, Murke, and Suckfüll, *Annalen*, 1931, **488**, 91).

This is the first recorded occurrence af a tetraethenoid steroid in Nature and also the first example of a naturally occurring sterol with olefinic unsaturation at position 14(15).

Experimental.

M. p.s are uncorrected. Unless specified to the contrary, rotations were determined in carbon tetrachloride at room temperature (15—25°) in a 1-dm. tube. For polarimetry all specimens were dried *in vacuo* at 20° below their m. p.s or at 110°, whichever was the lower. Values of $[\alpha]_D$ have been approximated to the nearest degree.

Absorption spectra were determined, unless specified to the contrary, in absolute ethanol by a Unicam S.P. 500 spectrophotometer.

Savory and Moore's standardised alumina was used throughout, unless specifically indicated to the contrary.

Light petroleum refers in all cases to the fraction of b. p. 40—60°.

In the text below, the phrase " in the usual way " refers to dilution with water, extraction with ether, washing successively with aqueous potassium hydroxide, aqueous hydrochloric acid, and water, followed by evaporation of the ethereal solution *in vacuo*. Where necessary, water was removed from the residue by azeotropic distillation with benzene *in vacuo*.

Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30—60 minutes in methanol or dioxan–methanol according to the solubility of the ester.

Raw Material.—The sample of " ergosterol " from the new strain of *A. niger*, kindly supplied by Messrs. J. and E. Sturge Ltd. through the courtesy of Dr. E. R. S. Winter, had m. p. 156—160°, $[\alpha]_D$ −150° (*c*, 1·06), compared with $[\alpha]_D$ −135° (*c*, 0·59) for pure ergosterol. The absorption spectrum of the crude sterol showed the triple maxima characteristic of ergosterol, the intensity corresponding to 82 ± 3% of ergosterol. The maximum at 320 mμ indicative of 14-dehydroergosterol (see below) corresponded to a content of 13%. The total sterols accounted for thus amounted to 95 ± 3%.

Isolation of 14-Dehydroergosterol.—Preliminary experiments failed to show any marked separation of 14-dehydroergosterol on crystallisation of the sterols or their acetates, or on careful chromatography of the latter. The first fraction of the chromatogram (11 fractions in all) had m. p. 171—172°, $[\alpha]_D$ −92° (*c*, 7·33) in chloroform, and was identified as pure ergosteryl acetate. The 14-dehydroergosteryl acetate was more strongly adsorbed. For example the penultimate fraction had m. p. 166—168° $[\alpha]_D$ −180° (*c*, 5·00) in chloroform (see below) and contained, according to the absorption spectrum, 57% of ergosteryl acetate. Fractional precipitation with digitonin indicated that 14-dehydroergosterol formed an insoluble digitonide similar to that given by ergosterol.

The following procedure was ultimately adopted for the separation of 14-dehydroergosterol (as the benzoate). Crude ergosterol (see above) (125 g.) was dissolved with heating in 1 l. of benzene with addition of 150 ml. of dry " technical pyridine." After the mixture had been cooled to room temperature benzoyl chloride (150 ml.) was added with further cooling. After the whole had been left overnight at room temperature water was added and the precipitated crude benzoate filtered off. The benzene layer of the filtrate was separated and a further quantity of crude benzoate precipitated by the addition of an equal volume of alcohol. The combined benzoate fractions were recrystallised eight times from benzene, to give a product (3·5 g.) melting at approx. 205° (decomp.), with $[\alpha]_D$ between −230° and −250° (*c*, approx. 0·5). Four further recrystallisations gave pure *14-dehydroergosteryl benzoate* (*ca.* 0·5 g.), m. p. 210—212° (decomp.), $[\alpha]_D$ −260° (*c*, 0·49), −274° (*c*, 3·04) in chloroform, $\lambda_{max.}$ 319 mμ, $\varepsilon_{max.}$ 16,000 (Found: C, 84·2; H, 9·4. $C_{35}H_{48}O_2$ requires C, 84·25; H, 9·3%). The m. p. is not sharp and depends on the rate of heating; the same applies to the simple derivatives.

During early experiments on the fractionation of the mixed benzoates, solvent mixtures containing chloroform were employed. Owing to acidity of the chloroform, the results were erratic and on some occasions no 14-dehydroergosteryl benzoate could be isolated. There was, further, difficulty during polarimetry with chloroform which was some months old. In one case 14-dehydroergosteryl benzoate mutarotated in 19 hours at room temperature from $[\alpha]_D$ −75° (after 1 hour in chloroform) to $[\alpha]_D$ +60°. The dextrorotatory product was shown to be a hydrocarbon but was not investigated further. Since 14-dehydroergosteryl benzoate was stable in carbon tetrachloride this solvent was used subsequently for polarimetry.

Alkaline hydrolysis of 14-dehydroergosteryl benzoate in the usual way caused much resinification. Reductive hydrolysis by lithium aluminium hydride proved satisfactory. Because of its sparing solubility in ether the benzoate was extracted from a Soxhlet thimble into ether containing an excess of lithium aluminium hydride. Addition of water, extraction with dilute sulphuric acid, and evaporation of the dried (Na_2SO_4) ethereal solution to small volume gave fine needles, m. p. 195—200° (decomp.), $[\alpha]_D$ −351° (*c*, 0·31). Two recrystallisations from carbon tetrachloride–methanol afforded pure *14-dehydroergosterol*, m. p. 198—201° (decomp.), $[\alpha]_D$ −396° (*c*, 0·21; *l* = 2-dm.), $\lambda_{max.}$ 319 mμ, $\varepsilon_{max.}$ 17,500 (Found : C, 85·6; H, 10·7. $C_{28}H_{42}O$ requires C, 85·2; H, 10·75%).

Acetylation in pyridine–acetic anhydride overnight at room temperature gave *14-dehydroergosteryl acetate*, crystallising as needles (from benzene–methanol), m. p. 164—167° (decomp.), $[\alpha]_D$ −322° (*c*, 0·11; *l* = 2 dm.), $\lambda_{max.}$ 319 mμ, $\varepsilon_{max.}$ 15,000 (Found : C, 82·2; H, 9·85. $C_{30}H_{44}O_2$ requires C, 82·5; H, 10·15%).

Benzoylation of 14-dehydroergosterol regenerated the benzoate, $[\alpha]_D$ −257° (*c*, 0·11; *l* = 2-dm.), $\lambda_{max.}$ 319 mμ, $\varepsilon_{max.}$ 16,000.

14-Dehydroergosteryl Benzoate–Maleic Anhydride Adduct.—In a preliminary experiment the crude acetate was refluxed with maleic anhydride in benzene solution. After hydrolysis and re-acetylation of the neutral material pure ergosteryl acetate, m. p. 172—174°, $[\alpha]_D$ −92° (*c*, 2·09 in chloroform), was readily obtained. The facility of reaction with maleic anhydride thus indicated was confirmed as follows. 14-Dehydroergosteryl benzoate (0·7 g.) was refluxed in benzene (10 ml.) with freshly distilled maleic anhydride (0·25 g.) for 3 hours. On cooling, the crystalline adduct was deposited. Recrystallisation from benzene gave felted needles of the *adduct*, m. p. 235—240° (decomp.), $[\alpha]_D$ −96° (*c*, 1·93; *l* = 4-dm.), no selective absorption in the region above 235 mμ (Found : C, 78·5; H, 8·05. $C_{39}H_{44}O_5$ requires C, 78·5; H, 8·1%).

In perbenzoic acid titration in chloroform at 0—5° two equivalents of per-acid were rapidly consumed. After 3 days the uptake corresponded to 2·4 equivalents.

Ozonolysis. The adduct (1·0 g.), suspended in acetic acid (50 ml.), was treated with ozonised oxygen for 3 hours until all had dissolved. The reaction mixture was diluted with water (50 ml.) and heated for 10 minutes whilst zinc dust was added. The solution was heated to boiling. 20 Ml. of distillate were collected and treated with semicarbazide hydrochloride (1 g.), and sodium hydrogen carbonate was added (to excess). After cooling at 0—5° overnight the semicarbazone was filtered off; recrystallised from benzene–light petroleum, it had m. p. 133—134°, $[\alpha]_D$ −44° (*c*, 1·05 in chloroform). There was no depression in m. p. on admixture with an authentic specimen of (−)-2 : 3-dimethylbutanal semicarbazone, m. p. 133—134°, $[\alpha]_D$ −47° (*c*, 1·03 in ethanol), −39° (*c*, 1·09 in chloroform), prepared in the same way from " α "-dihydroergosteryl acetate.

Hydrogenation of 14-Dehydroergosteryl Benzoate.—Pure 14-dehydroergosteryl benzoate (325 mg.) in anhydrous ether (125 ml.) was added to " AnalaR " acetic acid (100 ml.) and pre-reduced platinum catalyst (200 mg.), and the whole hydrogenated overnight. Working up in the usual way gave, after digestion with methanol, " α "-ergostenyl hexahydrobenzoate (320 mg.), m. p. 128—130°. One recrystallisation from chloroform–methanol furnished the pure hexahydrobenzoate (230 mg.), $[\alpha]_D$ +4° (*c*, 1·77 in chloroform), m. p. 134—135° alone or mixed with an authentic specimen (see below).

" α "-Ergostenyl Hexahydrobenzoate [with J. D. Cox and E. Miller].—Hydrogenation overnight of " α "-ergostenyl benzoate, ergosteryl benzoate, or ergosteryl B_3 benzoate, in acetic acid over a platinum catalyst, in each case afforded *" α "-ergostenyl hexahydrobenzoate* which, crystallised from ethyl acetate–methanol, had m. p. 134—135°, $[\alpha]_D$ +3° (*c*, 1·32 in chloroform) (Found : C, 82·1; H, 11·2. $C_{35}H_{58}O_2$ requires C, 82·3; H, 11·4%).

The constitution assigned to this compound was confirmed by alkaline hydrolysis which furnished " α "-ergostenol and hexahydrobenzoic acid, both giving no depression in m. p. on admixture with synthetic specimens of the same m. p.s.

Ergosteryl B_3 Benzoate–Maleic Anhydride Adduct [with J. D. Cox].—Ergosteryl B_3 benzoate (1 g.) in dry benzene (25 ml.) was refluxed with excess of maleic anhydride for 30 minutes. The crystalline *adduct* was rapidly deposited. Recrystallised from benzene, it had m. p. 262° (decomp.), $[\alpha]_D$ −62° (*c*, 0·55 in chloroform) (Found : C, 78·8; H, 8·35. $C_{39}H_{50}O_5$ requires C, 78·2; H, 8·4%).

Hydrogenation. Hydrogenation of this adduc tin acetic acid in the presence of a platinum catalyst and working up in the usual way afforded the dihydroergosteryl B_3 hexahydrobenzoate–maleic anhydride *adduct*, m. p. 217—220° (from chloroform–methanol), $[\alpha]_D$ −32° (*c*, 2·22 in chloroform; *l* = 0·5 dm.) (Found : C, 76·6; H, 9·4. $C_{39}H_{58}O_5$ requires C, 77·2; H, 9·65%).

Hydrogenation of 14-Dehydroergosteryl Benzoate–Maleic Anhydride Adduct.—Hydrogenation in acetic acid with a platinum catalyst and working up in the usual way also gave dihydroergosteryl B_3 hexahydrobenzoate–maleic anhydride adduct, m. p. 220—222° (from chloroform–light petroleum), $[\alpha]_D$ −28° (*c*, 1·74 in chloroform; *l* = 0·5 dm.), undepressed in m. p. on admixture with the authentic specimen (see above).

Ergosta-4 : 6 : 8(14) : 22-*tetraen*-3-*one*.—14-Dehydroergosterol (0·65 g.) was dissolved in dry acetone (25 ml.)–benzene (25 ml.) with addition of aluminium *tert.*-butoxide (2·0 g.). The solution was refluxed for 4 hours, then poured into cold dilute sulphuric acid, and the benzene layer separated and washed with water. After removal of the benzene *in vacuo*, the gummy residue was dissolved in light petroleum and chromatographed over alumina. Benzene–ether (9 : 1) eluted crystalline ergosta-4 : 6 : 8(14) : 22-tetraen-3-one which, recrystallised from methanol or light petroleum, had m. p. 114—115°, $[\alpha]_D$ +590° (*c*, 0·21 in chloroform; *l* = 2 dm.), $\lambda_{max.}$ 348 mμ, $\varepsilon_{max.}$ 26,500 (Found: C, 85·1; H, 10·4. $C_{28}H_{40}O$ requires C, 85·65; H, 10·25%).

In ethanolic hydrochloric acid the ketone gave the corresponding 2 : 4-*dinitrophenylhydrazone* as very dark red needles, purified by chromatography and recrystallisation from ethyl acetate; it had m. p. 236—237° decomp., $\lambda_{max.}$ 427 mμ, $\varepsilon_{max.}$ 41,000 in chloroform (Found: N, 10·2. $C_{34}H_{44}O_4N_4$ requires N, 9·95%).

Reduction of 14-*Dehydroergosteryl with Sodium and* n-*Propanol*.—14-Dehydroergosteryl benzoate (2 g.) was added to boiling *n*-propanol (100 ml.) in which several atomic proportions of sodium had been dissolved. When hydrolysis was complete (0·5 hour) more sodium was added until the *n*-propanol was saturated (4 hours). Dilution with water, extraction with ether, and working up in the usual way gave a mixture which was then benzoylated and combined with the benzoates from the reduction of a further 2·0 g. of 14-dehydroergosteryl benzoate. The benzoate mixture, crystallised once from chloroform–methanol, had $[\alpha]_D$ −92° (*c*, 0·58 in chloroform), $\lambda_{max.}$ 250, 280, and 293 mμ, $\varepsilon_{max.}$ 9000, 1500, and 480 respectively (as well as benzoate absorption). The last two maxima were clearly due to about 10% of ergosteryl benzoate. There was no absorption at 320 mμ and the reduction was therefore substantially quantitative. The mixed benzoates were refluxed in benzene (5 ml.) with maleic anhydride (0·4 g.) for 3 hours. Concentration of the benzene solution *in vacuo* and extraction of unreacted maleic anhydride with water afforded, in small yield, ergosteryl B_3 benzoate–maleic anhydride adduct, m. p. 262° (decomp.) alone or mixed with an authentic specimen (see above), $[\alpha]_D$ −54° (*c*, 0·50 in chloroform).

The residual benzoates were carefully chromatographed in light petroleum over alumina, the progress of the fractionation being followed by both rotation and absorption spectrum. Benzene–light petroleum (1 : 3) eluted material not of relevant interest. Benzene–light petroleum (1 : 1) then eluted material which was collected in five fractions. The last of these contained (absorption spectrum) about 50% of ergosteryl benzoate. Material from the other four, in which the conjugated diene ($\lambda_{max.}$ 252 mμ) had been concentrated, was combined and recrystallised from chloroform–methanol, to give *ergosta*-6 : 8(14) : 22-*trien*-3β-*yl benzoate*, m. p. 129—130°, $[\alpha]_D$ −104° (*c*, 2·13 in chloroform), $\lambda_{max.}$ 234 and 252 mμ, $\varepsilon_{max.}$ 23,000 and 21,500 respectively (Found: C, 83·9; H, 10·05. $C_{35}H_{48}O_2$ requires C, 83·95; H, 9·9%).

Alkaline hydrolysis afforded *ergosta*-6 : 8(14) : 22-*trien*-3β-*ol*, m. p. 113—114° (from methanol), $[\alpha]_D$ −115° (*c*, 2·10 in chloroform), $\lambda_{max.}$ 253 mμ, $\varepsilon_{max.}$ 17,000 (Found: C, 78·3; H, 10·45. $C_{28}H_{44}O,2CH_3{\cdot}OH$ requires C, 78·2; H, 11·4%).

Acetylation with pyridine–acetic anhydride overnight gave the corresponding *acetate*, m. p. 113—114° (from methanol), $[\alpha]_D$ −107° (*c*, 1·98 in chloroform) $\lambda_{max.}$, 253 mμ, $\varepsilon_{max.}$ 17,000 (Found: C, 82·3; H, 10·85. $C_{30}H_{44}O_2$ requires C, 82·15; H, 10·55%).

Treatment of ergosta-6 : 8(14) : 22-trien-3β-yl benzoate (200 mg.) in chloroform with dry hydrogen chloride at 0° for 10 minutes (cf. Barton and Brooks, *J.*, 1951, 277) and working up in the usual way gave crude ergosteryl B_3 benzoate. This was refluxed in benzene (3 ml.) for 3 hours with maleic anhydride (40 mg.). After cooling, water was added and the mixture left overnight. The crystals deposited were recrystallised twice from benzene, to give ergosteryl B_3 benzoate–maleic anhydride adduct, m. p. 260—261° alone or mixed with an authentic specimen (see above), $[\alpha]_D$ −55° (*c*, 0·51 in chloroform).

Hydrogenation of ergosta-6 : 8(14) : 22-trien-3β-yl acetate (100 mg.) in acetic acid overnight over a platinum catalyst and working up in the usual way furnished "α"-ergostenyl acetate, $[\alpha]_D$ ±0° (*c*, 1·74 in chloroform), m. p. 109—110° (from chloroform–methanol) alone or mixed with an authentic specimen of the same m. p. and rotation (Barton and Cox, *J.*, 1948, 783).

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BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, April 17th*, 1951.]

608. *The Halogen Cations in Aqueous Solution.*

By R. P. Bell and E. Gelles.

Thermodynamic and other physicochemical data on iodine, bromine, and chlorine have been used in the calculation of several new thermodynamic quantities. These include the free energies of formation in aqueous solution of the halogen cations X^+ and $\overset{+}{H_2O}X$ (X = I, Br, Cl).

Electrometric measurements have been made on aqueous solutions of iodine in the presence of varying concentrations of silver salts and acid. It has been shown that, under certain experimental conditions, solutions containing considerable concentrations of an iodine cation can be prepared. The free energy of ionisation of iodine at 25° is found to be 15 kcal./mole, in good agreement with the free energy calculated for the reaction $I_2 + H_2O = \overset{+}{H_2O}I + I^-$.

Although the cations of the halogens are now frequently invoked as agents in halogenation reactions, little evidence has so far been produced for their existence in measurable concentration in aqueous solution (Hinshelwood, *J.*, 1947, 694; De La Mare, Hughes, and Vernon, *Research*, 1950, **3**, 192; Derbyshire and Waters, *J.*, 1950, 564; Sidgwick, "The Chemical Elements and their Compounds," Oxford Univ. Press, 1950, Vol. II, p. 1240). In this paper theoretical and experimental studies on the halogen cations are presented.

Section A. Theoretical Considerations.

An attempt has been made in this section to calculate the thermodynamic tendency for various halogen cations to be formed in aqueous solution. Throughout this paper, the symbol X stands for I, Br, and Cl; all thermodynamic data refer to 25° unless otherwise stated.

In the gas phase the tendency for halogen molecules to ionise with the formation of X^+ is extremely small. The Gibbs free energy ΔG of the reaction

$$X_{2\,gas} = X^+_{gas} + X^-_{gas}$$

is 195, 231, and 263 kcal./mole for iodine, bromine, and chlorine. These values are obtained from the known free energies of dissociation, ionisation potentials, and electron affinities (National Bureau of Standards, Washington, D.C.).

The tendency to ionisation increases enormously in aqueous solution because of the large heats of solution of the ions. The heats and free energies of solution of ions are obtained by one of the following methods. The free energies of solution of many salts have been obtained directly by experiment. The data for pairs of ions thus obtained can be analysed for single ions if a value for any one ion is assumed. The entropies of solution of ions are referred to the entropy of solution of the proton. The heats of solution of ions of equal charge and size are usually taken as equal. For example, the experimental values for potassium fluoride (radii of K^+ and F^- are equal) provide a key for the heats of solution of many other single ions. It has, however, been shown theoretically that a negative univalent ion has a heat of solution about 2% higher than a positive ion of equal radius (Bernal and Fowler, *J. Chem. Physics*, 1933, **1**, 515). The heats and entropies of solution of ions, obtained by this sort of analysis of experimental data, are in good agreement with the results of the *a priori* calculations by Eley and Evans (*Trans. Faraday Soc.*, 1938, **34**, 1093). The free energies of solution of the ions X^- are taken from this paper. It will be seen later that the free energies of solution of X^+ and $\overset{+}{H_2O}X$ can be estimated in a similar manner.

We can now consider the tendency for the ionisation process (A) to occur in aqueous solution.

(A) $$X_{2\,aq.} \overset{\Delta G(A)}{=} X^+_{aq.} + X^-_{aq.}$$

$$\begin{array}{ccccc} X_{2\,gas} & \xrightarrow{b} & 2X_{gas} & \xrightarrow{c} & X^+_{gas} + X^-_{gas} \\ \uparrow a & & & & \downarrow d \quad \downarrow e \\ X_{2\,aq.} & & \xrightarrow{\Delta G(A)} & & X^+_{aq.} + X^-_{aq.} \end{array}$$

$$\Delta G(A) = \Delta G_a + \Delta G_b + \ldots + \Delta G_e.$$

The free energies for steps *a*, *b*, and *c* are well known. The free energies of solution of the ions in steps *d* and *e* are obtained by the method described above. The radii of the ions X^+ can

be estimated from Pauling's data (" Nature of the Chemical Bond," Cornell, 1944) as 1·13, 0·96, and 0·84 Å for iodine, bromine, and chlorine. If the ions are spherical, their free energies of solution are estimated as −98, −111, and −120 kcal. It is almost certain that in aqueous solution the incomplete electron shell of these ions will be completed by a water molecule, giving ions of the type $H_2\overset{+}{O}X$. It is, however, of interest to consider what the ionising tendency would be if the cations were the bare ions X^+ and were solvated by coulombic forces only.

We then have $\Delta G(A) = \Delta G_a + \Delta G_b + \ldots + \Delta G_g$.

For iodine, $\Delta G(A) = 0{\cdot}7 + 28{\cdot}9 + (242{\cdot}2 - 75{\cdot}7) - 98 - 43 = 55$ kcal.

For bromine, $\Delta G(A) = -0{\cdot}2 + 38{\cdot}6 + (274{\cdot}6 - 82{\cdot}1) - 111 - 53 = 67$ kcal.

For chlorine, $\Delta G(A) = -1{\cdot}0 + 50{\cdot}4 + (300{\cdot}3 - 87{\cdot}3) - 120 - 58 = 84$ kcal.

These values correspond to equilibrium constants $[X^-][X^+]/[X_2]$ of 10^{-40}, 10^{-50}, and 10^{-60}. The values for the free energies of solution of the positive ions X^+ are of course approximate, but there can be no doubt that these bare cations cannot exist in appreciable concentration in aqueous solution.

A considerable stabilisation of the cations occurs when the covalent bond to a water molecule is formed and ions of the type $H_2\overset{+}{O}X$ are produced. It will be seen later that the free energies of solution of the cations $H_2\overset{+}{O}X$ and X^+ are nearly equal, so that the stabilisation that occurs is mainly due to the free energy of formation of the oxygen–halogen bond.

Free Energies of Formation of Oxygen–Halogen Bonds.—The free energies of formation of the oxygen–halogen bonds in the compounds HOX (gas) can be calculated from the following thermodynamic cycle :

$$X_{2\,aq.} + H_2O_{liq.} \overset{\Delta G}{=} X^-_{aq.} + H^+_{aq.} + HOX_{aq.}$$

$$X_{2\,aq.} \xrightarrow{a} X_{2\,gas} \xrightarrow{b} X_{gas} + X_{gas};\ X_{gas} + H_{gas} \xrightarrow{g} H^+_{aq.} + X^-_{aq.}$$

$$H_2O_{liq.} \xrightarrow{c} H_2O_{gas} \xrightarrow{d} H_{gas} + OH_{gas};\ OH_{gas} + X_{gas} \xrightarrow{f} HOX_{gas}$$

$$HOX_{gas} \xrightarrow{t} HOX_{aq.}$$

The free energy ΔG of the hydrolysis reaction is the sum of the free energy changes *a*—*g*. The data used for this cycle are taken mainly from the tables of the National Bureau of Standards. The free energies of hydrolysis of the halogens have been measured by several workers (Bray and Conolly, *J. Amer. Chem. Soc.*, 1911, **33**, 1485; Liebhafsky, *ibid.*, 1934, **56**, 1500; Jakowkin, *Z. physikal. Chem.*, 1899, **29**, 613).

For iodine, $\Delta G = 17{\cdot}0 = 0{\cdot}7 + 28{\cdot}9 + 2{\cdot}0 + 112{\cdot}2 - 77{\cdot}7 + \Delta G_f + \Delta G_g$
$\Delta G_f + \Delta G_g = -49{\cdot}1$ kcal.

For bromine, $\Delta G = 11{\cdot}2 = -0{\cdot}2 + 38{\cdot}6 + 2{\cdot}0 + 112{\cdot}2 - 92{\cdot}8 + \Delta G_f + \Delta G_g$
$\Delta G_f + \Delta G_g = -48{\cdot}6$ kcal.

For chlorine, $\Delta G = 4{\cdot}5 = -1{\cdot}0 + 50{\cdot}4 + 2{\cdot}0 + 112{\cdot}2 - 105{\cdot}1 + \Delta G_f + \Delta G_g$
$\Delta G_f + \Delta G_g = -54{\cdot}0$ kcal.

The free energy of solution of HOX_{gas}, ΔG_g, can be estimated by comparison with the free energies of solution of the halogens $X_{2\,gas}$ and the free energy of condensation of water H_2O_{gas}. ΔG_g is considered to be -2 ± 1 kcal./mole for all three halogens.

Hence, we obtain the values for ΔG_f, the free energies of formation of the oxygen–halogen bonds :

$HO_{gas} + I_{gas} = HOI_{gas}$; $\Delta G_f = -47$ kcal.

$HO_{gas} + Br_{gas} = HOBr_{gas}$; $\Delta G_f = -47$ kcal.

$HO_{gas} + Cl_{gas} = HOCl_{gas}$; $\Delta G_f = -52$ kcal.

Free Energies of Formation of $H_2\overset{+}{O}X$ *in Aqueous Solution.*—We can now turn to the calculation of the free energy of formation of the cation $H_2\overset{+}{O}X$ in aqueous solution. The free energy of the reaction (B), $\Delta G(B)$, is the sum of the free energies of steps *a*—*g* :

$$\text{(B)} \qquad X_{2\,aq.} + H_2O_{liq.} \overset{\Delta G(B)}{=} H_2\overset{+}{O}X_{aq.} + X^-_{aq.}$$

$$X_{2\,aq.} \xrightarrow{a} X_{2\,gas} \xrightarrow{b} X_{gas} + X_{gas} \xrightarrow{c} X^+_{gas} + X^-_{gas}$$

$$H_2O_{liq.} \xrightarrow{d} H_2O_{gas}\,X^+_{gas} + H_2O_{gas} \xrightarrow{e} H_2\overset{+}{O}X_{gas} \xrightarrow{f} H_2\overset{+}{O}X_{aq.}$$

$$X^-_{gas} \xrightarrow{g} X^-_{aq.}$$

We must consider the free energies of steps *e* and *f*. For the free energies of step *e*, the calculated free energies for the reaction $X_{gas} + OH_{gas} = HOX_{gas}$ are used.

The analogous reactions of the proton are as follows : $H^+_{gas} + H_2O_{gas} \longrightarrow H_3O^+_{gas} \longrightarrow H_3O^+_{aq.}$. The heat of solution of H^+_{gas} is 282 kcal. (Baughan, *J.*, 1940, 1403). If the heat of formation of $H_3O^+_{gas}$ is equal to the heat of the reaction $H_{gas} + OH_{gas} = H_2O_{gas}$ (120 kcal.), the heat of solution of $H_3O^+_{gas}$ is 162 kcal. By analogy with H_3O^+, and from consideration of their size, the heats and free energies of solution of the ions $H_2\overset{+}{O}X$ are estimated as follows (cf. Eley and Evans, *loc. cit.*) :

	$H_2\overset{+}{O}I$	$H_2\overset{+}{O}Br$	$H_2\overset{+}{O}Cl$
Q (heat evolved)	100	110	120
ΔG_f	−94	−103	−112

It is possible that the free energies ΔG_e are underestimated. However, in that case the heats and free energies of solution of the ions $H_3\overset{+}{O}$ and $H_2\overset{+}{O}X$ are overestimated proportionally.

The free energy of reaction (B) is given by the relation $\Delta G(B) = \Delta G_a + \Delta G_b + \ldots + \Delta G_g$:

For iodine, $\Delta G(B) = 0{\cdot}7 + 28{\cdot}9 + (242{\cdot}2 - 75{\cdot}7) + 2{\cdot}0 - 47 - 94 - 43 = 14$ kcal.

For bromine, $\Delta G(B) = -0{\cdot}2 + 38{\cdot}6 + (274{\cdot}6 - 82{\cdot}1) + 2{\cdot}0 - 47 - 103 - 53 = 30$ kcal.

For chlorine, $\Delta G(B) = -1{\cdot}0 + 50{\cdot}4 + (300{\cdot}3 - 87{\cdot}3) + 2{\cdot}0 - 52 - 112 - 58 = 42$ kcal.

The equilibrium constants $K = [H_2\overset{+}{O}X][X^-]/[X_2]$ corresponding to the above free-energy changes at 25° are approximately 10^{-10} for iodine, 10^{-30} for bromine, and 10^{-30} for chlorine.

The free energies ΔG_e and ΔG_f are admittedly somewhat uncertain, but the above values of the equilibrium constants are considered reliable to within a few powers of ten.

The conclusions that can definitely be drawn from the above calculations are as follows :

(1) The bare halogen cations X^+ cannot exist in appreciable concentration in aqueous solution.

(2) The hydrated halogen cations $H_2\overset{+}{O}X$ are much more stable. The iodine cation $H_2\overset{+}{O}I$ is the only one, however, which appears to be sufficiently stable to allow preparation of a halogen solution in which an appreciable proportion of the halogen is present as a cation. Thus, if the iodide concentration in an iodine solution were lowered to 10^{-12}N. by addition of a soluble silver salt, the calculated value for the equilibrium constant indicates that almost all the iodine in solution will be in the form of the cation $H_2\overset{+}{O}I$ (provided no other reactions interfered; see below). On the other hand, in the case of bromine and chlorine, even at the lowest controllable halide concentrations, the calculations indicate that $[H_2\overset{+}{O}X]/[X_2] \ll 1$.

The experimental studies on the iodine cation presented in the following section confirm the theoretical predictions for this halogen, and lend strong support to the validity of the thermodynamic calculations for the other halogens.

Section B. Experimental Studies on the Iodine Cation.

The calculations in the preceding section indicated that the stability of the hydrated iodine cation should permit an almost complete conversion of iodine into this cation at attainably low iodide concentrations. This conclusion has been confirmed by the experiments now to be described.

When iodine is dissolved in water, the ionisation (1) can be followed by a variety of reactions :

$$(1) \quad I_2 + H_2O = H_2\overset{+}{O}I + I^-.$$

$$(2) \quad H_2\overset{+}{O}I + H_2O = HOI + H_3O^+.$$

$$(3) \quad 3HOI + 3H_2O = IO_3^- + 2I^- + 3H_3O^+.$$

$$(4) \quad I_2 + I^- = I_3^-, \text{ etc.}$$

Formation of $H_2\overset{+}{O}I$ is clearly favoured by a low iodide concentration. A low iodide concentration represses reactions of type (4); however, it facilitates the hydrolytic reactions (2, 3). The latter can be repressed by increasing the acid concentration; acid has no effect on the ionisation equilibrium (1). It is clear that the concentration of the iodine cation which can be produced is limited not only by its free energy of formation, but also by the free energies and velocities of the subsequent hydrolytic decompositions. For these latter reactions the following data are available.

Steps (1) and (2) in the above reaction scheme are generally represented by (5) :

$$(5) \quad I_2 + H_2O = HOI + I^- + H^+.$$

The equilibrium constant of this hydrolysis reaction is 3×10^{-13} (Bray and Conolly, *loc. cit.*) and the reaction is very fast (Liebhafsky, *Z. physikal. Chem.*, 1931, **155**, *A*, 289).

The formation of iodate is generally represented by reaction (6) :

$$(6) \quad 3I_2 + 3H_2O = IO_3^- + 5I^- + 6H^+.$$

The equilibrium constant is 4×10^{-48} (Lundberg, Vestling, and Ahlberg, *J. Amer. Chem. Soc.*, 1937, **59**, 264). This reaction is very slow at appreciable iodide and acid concentrations. The rate of the iodate–iodide reaction at low iodide concentrations is given by the equation $-d[IO_3^-]/dt = 2 \times 10^4[IO_3^-][I^-][H^+]_2$ moles $l.^{-1}$ $min.^{-1}$ (Abel, *Z. physikal. Chem.*, 1928, **136**, 186 *et seq.*). Combining this expression with the equilibrium data, we have for the initial rate of iodate formation

$$(7) \quad d[IO_3^-]/dt \simeq 8 \times 10^{-44} [I_2]^3/[I^-]^4[H^+]^4 \text{ moles } l.^{-1} \text{ } min.^{-1}.$$

on the assumption that the system follows the same kinetics on both sides of the equilibrium.

The equilibrium constant of reaction (5) and the rate of reaction (6) determine the concentrations of iodine, iodide, and acid for which the hydrolytic decompositions of the iodine cation can be repressed.

Preparation and Investigation of Solutions containing $H_2\overset{+}{O}I$.—Solutions of iodine were prepared in which the iodide concentration was lowered by the addition of a soluble silver salt, and the removal of iodine (either by ionisation or by hydrolytic decomposition) was investigated by measuring the redox potentials of the solutions. Cells of the following type were employed.

$$\underset{\text{Solution 1.}}{Pt, I_2, Ag^+, H^+} \;|\; \text{Satd. } KNO_3 \;|\; \underset{\text{Solution 2.}}{I^-, I_2, H^+, Pt}$$

The acid concentrations and ionic strengths were always equal in solutions 1 and 2. The activity coefficients of the iodide ion in the two solutions can therefore be assumed equal, and the liquid-junction potential will be negligible. The E.M.F. of the experimental cell is then given by the expression

$$(8) \quad \text{E.M.F.} = (RT/2F)\,(\ln [I^-]_2^3/[I_2]_2 - \ln [I^-]_1^3/[I_2]_1)$$

where the subscripts refer to solutions 1 and 2.

If further hydrolytic changes are effectively repressed, ionisation is the only process by which molecular iodine is removed :

$$\begin{array}{ccccc} I_2 & + & H_2O & = & H_2\overset{+}{O}I + I^- \\ a - x & & & & x \quad S/f_\pm^2(b - x) \end{array}$$

a and b are the initial concentrations of iodine and silver, respectively, in solution 1, x is the concentration of the cation at equilibrium, S the solubility product of silver iodide, and $f_\pm$ the mean ionic activity coefficient, where $[Ag^+][I^-]f_\pm^2 = S$. Inserting the appropriate values, we have for the E.M.F. in volts at 25° :

$$\text{E.M.F.} = 0{\cdot}0296\,(\log_{10} [I^-]_2^3/[I_2]_2 - \log_{10} [S^2/f_\pm^4(b - x)^2(a - x)])$$

and on rearrangement of the equation :

$$(9)\quad \log_{10}(b-x)^3(a-x) = \frac{\text{E.M.F.}}{0{\cdot}0296} - \log_{10}\frac{[I^-]_2^3}{[I_2]_2} + \log_{10}S^3 - \log_{10}f_\pm^4$$

If the activity coefficients are known, the above equation can be solved for the unknown x, and hence the thermodynamic ionisation constant K can be obtained :

$$(10)\quad K = \frac{[\overset{+}{H_2O}I][I^-]f_\pm^2}{[I_2]} = \frac{x\left[\dfrac{S}{f_\pm^2(b-x)}\right]f_\pm^2}{a-x} = \frac{xS}{(b-x)(a-x)}$$

Experimental.

The electromotive force cell was similar in design to that used by Everett and Wynne-Jones (*Proc. Roy. Soc.*, 1938, *A*, **169**, 190 *et seq.*). Platinum-gauze electrodes fitted into the two electrode compartments, which were connected with the salt bridge compartment by thin tubes ending in jets; the liquid junctions were formed in these jet tubes. The E.M.F. was measured with a Tinsley Vernier potentiometer. All measurements were made at 25° ± 0·02°. Conductivity water and reagents of analytical grade were used throughout. For each experiment two solutions were made. Solution 1 contained known concentrations of iodine, silver nitrate, and perchloric acid. Solution 2 contained known concentrations of perchloric, acid, iodine, and iodide, allowance being made for the iodine–tri-iodide equilibrium (Jones and Kaplan, *J. Amer. Chem. Soc.*, 1928, **50**, 1845). The ionic strength was adjusted, when necessary, with sodium perchlorate. The solutions were made up, the cell filled and brought to constant temperature in a thermostat, and the E.M.F. measured 5 minutes after mixing. Readings of E.M.F. were then taken at intervals for some time. The iodine solution for solution 1 was always freshly made by shaking AnalaR iodine with water and filtering through a sintered-glass filter. The iodine–iodide stock solutions for solution 2 were prepared by weight. Standard thiosulphate was used as the halogen standard, and constant-boiling hydrochloric acid as the acid–base standard. The platinum electrodes were washed repeatedly with water and heated in an alcohol flame before use.

Results.

Table I shows a set of typical experiments to determine the iodine ionisation constant. The initial iodine concentration and the iodide concentration are varied over nearly two powers of 10; the acid concentration range is 0·2—1·0N.

The activity coefficients are not known experimentally at these high concentrations. However, reasonable values can be calculated from the expression for the mean ionic activity coefficient (Davies, *J.*, 1938, 2093) :

$$(11)\quad -\log_{10}f_\pm = 0{\cdot}5I^{\frac{1}{2}}/(1+I^{\frac{1}{2}}) - 0{\cdot}2I$$

where I is the ionic strength of the solution. The solubility product of silver iodide is taken as $1{\cdot}0 \times 10^{-16}$ g.-ion/l. (Hass and Jellinek, *Z. physikal. Chem.*, 1932, **162**, 153). The last column in Table I gives the ionisation constants calculated as shown above from equations (9)—(11). The constants obtained are very good, especially in view of the nature of the solutions studied, in particular the uncertainties over activity coefficients, and the very low iodide concentrations in the presence of silver iodide.

The degree of constancy can be improved by employing a slightly different expression for the activity coefficients. In particular, in experiments such as the 4th and the 5th in the list, where both sodium perchlorate and perchloric acid are present in considerable concentrations, a lowering of the mean activity coefficient by the sodium salt improves the values for the ionisation constant. This decrease in $f_\pm$ is not unexpected (Pearce and Nelson, *J. Amer.Chem. Soc.*, 1933, **55**, 3075; Scatchard, Prentiss, and Jones, *ibid.*, 1934, **56**, 805).

The most important conclusion from these experiments is, however, that, regardless of the expression used for the activity coefficients (even $f_\pm = 1$ throughout), the ionisation constants show no trend with the concentration of any given species present in the solutions. If the removal of iodine were due to hydrolytic decomposition, the extent of this decomposition should of course be acid-dependent, so that an inverse variation of the apparent ionisation constant would be expected with acid concentration.

The thermodynamic ionisation constant of iodine is found to be $1{\cdot}2 \times 10^{-11}$. This value is in good agreement with that predicted in the preceding section for the reaction $I_2 + H_2O = \overset{+}{H_2O}I + I^-$. It is therefore certain that the cation under study is the hydrated cation or hypoiodous acidium ion and not the base cation I^+.

TABLE I.

Ionisation. (*Concentrations in g.-mols./litre.*)

E.M.F. values are initial values which generally remain steady for several hours.

$10^3[I_2]$, initial.	$10^3[Ag^+]$, initial.	$\log_{10}\frac{[I^-]_2^3}{[I_2]_2}$,	E.M.F. (volts).	I.	$f_\pm$.	$[H^+]$.	$10^3[H_2\overset{+}{O}I]$.	$10^{13}[I^-]$.	$10^3[I_2]$.	$10^{11}K$.
1·77	7·95	0·035	0·524	1·0	0·89	1·0	1·60	19·8	1·74	1·4
3·00	15·6	0·035	0·542	1·0	0·89	0·9	2·82	9·83	1·90	1·2
23·6	5·00	0·035	0·500	1·0	0·89	0·75	4·75	510	188	1·1
23·6	10·0	0·035	0·511	1·0	0·89	0·60	9·60	285	140	1·5
					(0·79)					(1·2)
23·6	5·00	0·035	0·485	1·0	0·89	0·40	4·86	914	187	1·9
					(0·76)					(1·3)
7·15	8·77	−0·965	0·502	1·0	0·89	1·0	5·70	41·1	14·5	1·3
2·26	5·85	−0·965	0·495	1·0	0·89	1·0	1·80	31·2	4·57	1·0
2·26	5·85	−0·965	0·488	0·75	0·83	0·75	1·91	36·8	3·47	1·4
18·7	5·00	−0·965	0·470	0·50	0·78	0·50	4·64	448	141	0·9
7·15	9·75	−0·965	0·501	0·50	0·78	0·50	5·82	42·0	13·3	1·1
2·26	5·85	−0·965	0·490	0·50	0·78	0·50	1·75	40·0	5·13	0·8
5·40	10·0	−0·965	0·474	0·40	0·77	0·40	9·75	690	443	0·9
3·75	10·0	−0·965	0·498	0·30	0·76	0·30	3·36	26·1	3·89	1·3
6·78	5·85	−0·965	0·482	0·30	0·76	0·30	4·34	115	24·5	1·2
18·7	5·00	−0·965	0·457	0·20	0·77	0·20	5·00	712	137	1·5

The equilibrium constant for reaction (2) (p. 2737) is obtained by dividing the hydrolysis constant for reaction (*b*) by the ionisation constant (1):

$$K_3 = \frac{[HOI][H_3O^+]}{[H_2\overset{+}{O}I]} = \frac{[H_3O^+][I^-][HOI]f_\pm^2}{[I_2]} \Big/ \frac{[H_2\overset{+}{O}I][I^-]f_\pm^2}{[I_2]} = 0{\cdot}03$$

hence

$$(12)\quad [H_2\overset{+}{O}I] \simeq 35[H_3\overset{+}{O}][HOI]$$

In the experiments recorded in Table I there is present a small concentration of hypoiodous acid, which decreases with increasing acid concentration. No correction for this equilibrium concentration of hypoiodous acid has been applied to the values listed in Table I. It can be seen from equation (12) that this correction will lead to a decrease in the $H_2\overset{+}{O}I$ concentration and in the ionisation constant ranging from approximately 3% when $[H^+] = 1{\cdot}0$N to 12% when $[H^+] = 0{\cdot}2$N.

TABLE II.

Iodate formation.

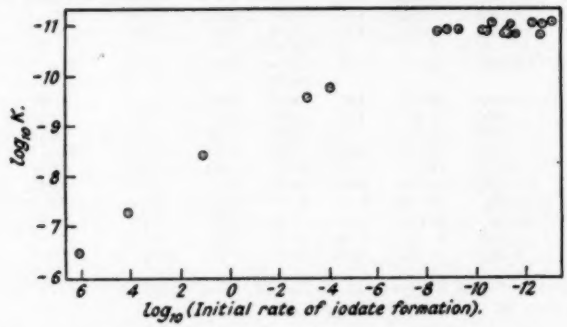
$10^3[I_2]$, initial.	$10^3[Ag^+]$, initial.	$\log_{10}\frac{[I^-]_2^3}{[I_2]_2}$,	E.M.F.† (volts).	$[H^+]$.	$f_\pm$.	$10^3[H\overset{+}{O}I]$.*	$10^{14}[I^-]$.*	$[I_2]$.*	K.*
5·0	0·24	0·04	0·515	0·1	0·79	5·0	84	$1{\cdot}6 \times 10^{-7}$	$1{\cdot}6 \times 10^{-10}$
5·0	0·36	0·04	0·515	0·1	0·79	5·0	51	$6{\cdot}0 \times 10^{-8}$	$2{\cdot}7 \times 10^{-10}$
4·7	0·36	−0·50	0·472	0·01	0·89	4·7	41	$3{\cdot}9 \times 10^{-9}$	$3{\cdot}9 \times 10^{-9}$
26	50	−2·56	0·465	1·0	0·89	26	0·25	$1{\cdot}1 \times 10^{-11}$	$4{\cdot}7 \times 10^{-9}$
29	50	−1·57	0·463	0·27	0·76	29	0·35	$1{\cdot}8 \times 10^{-12}$	$3{\cdot}2 \times 10^{-7}$

* Apparent concentrations. † Initial values.

Under the conditions of the experiments in Table I the rate of iodate formation given by equation (7) is negligible. When iodate equilibrium is attained after several days, considerable quantities of iodate have been formed, as is shown by the slow decrease of the E.M.F. with time from the steady value of the first few hours. In the experiments recorded in Table II, the iodide and/or acid concentrations have been deliberately lowered so as to accelerate the rate of iodate formation. It is observed that the apparent ionisation constants now vary with acid concentration in the manner expected for a hydrolytic reaction of this type.

In the figure, apparent ionisation constants are plotted against calculated rates of iodate formation. As long as the latter are small, the ionisation constants are fairly steady. When the rate of iodate formation becomes so fast that iodine is converted into iodate in a matter of hours or even more quickly, then a rapid fall in the apparent ionisation constants is observed. The fourth-power dependence of the rate of the iodate reaction on the iodide and acid concentrations places a sharp limit on the conditions under which solutions containing the cation $H_2\overset{+}{O}I$ can be studied.

Note on Previous Work.—One previous attempt to determine the iodine ionisation constant merits special discussion (Murray, *J.*, 1925, **127**, 882). The method employed was to measure electrometrically the iodide concentration in an acid solution of iodine. The iodide concentration found was attributed entirely to ionisation, and the ionisation constant was taken to be equal to $[I^-]^2 . f_\pm^2/I_2 = 1 \times 10^{-8}$ ($[I_2] = [I_2]$ initial). This method depends on (*a*) ionisation having a much greater tendency to occur than hydrolysis, and (*b*) the absence of iodide impurities.



Condition (*a*) is not adequately fulfilled except at high acid concentrations, as shown by the present work; nor does it appear that condition (*b*) is satisfied. It is unlikely that iodide impurities can have been eliminated in the previous work, as shown by some new experiments illustrated in Table III. The iodide concentrations in various acid solutions of iodine were

TABLE III.

Sample.*	$[H^+]$.	$10^3[I_2]$.	$10^4[I^-]$.	$100[I^-]/[I_2]$.	$10^3[I^-]^2 f_\pm^2/[I_2]$.
1	0·10	17·5	5·76	3·29	18·4
2	0·10	54·5	4·00	0·73	2·0
3	0·10	26·5	3·63	1·37	3·2
4	0·10	3·60	1·76	4·88	5·4
4	0·10	3·60	1·74	4·84	5·4
5	0·10	47·0	2·92	0·62	1·2
6	0·25	20·2	2·45	1·22	1·6

* 1. Iodine. 2, 3, 4. "AnalaR" Iodine. 5, 6. "AnalaR" Iodine freshly resublimed.

measured electrometrically. The apparatus, especially the electrodes, was washed repeatedly with conductivity water before use. The results show that the iodide concentration and the apparent ionisation constant depend on the sample of iodine used. The iodide concentration decreases with repeated purification of the iodine. It is concluded that this method is inapplicable to the study of the ionisation of iodine. The method developed in the present work is, of course, unaffected by small iodide impurities.

Conclusions.—It has been shown that the thermodynamic stability of the iodine cation in aqueous solution is governed essentially by the equilibrium constants of reactions (1), (2), and (3). The equilibrium constants of reactions (1) and (2) are found to be 1×10^{-11} and 3×10^{-2}, respectively. For practical purposes the third equilibrium condition (3) may be replaced by the condition that the rate of iodate formation must be sufficiently slow. This analysis of the factors governing the stability of the iodine cation should be of direct practical application in many iodination reactions, in which the iodine cation can be the active iodinating agent.

One of us (E. G.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant during the first part of this work, the Ramsay Memorial Fellowships Trust for the award of a Fellowship, and Professors E. D. Hughes, F.R.S., and C. K. Ingold, F.R.S., for the facilities of the Ramsay Laboratories.

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609. *Determination of Aldehydes in Combustion Products.*

By H. C. Bailey and J. H. Knox.

The standard methods of separately determining aldehydes in mixtures such as those obtained from combustion of hydrocarbons have proved unsatisfactory. A method is described in which the aldehydes are oxidised by silver oxide to the silver salts of fatty acids. The silver is determined volumetrically by potassium thiocyanate. Separation and determination of individual aldehydes is achieved by chromatography of the acids which can be liberated from the silver salts. The method has been successfully applied to the identification and determination of the aldehydes formed during the oxidation of higher hydrocarbons.

During research into the products of hydrocarbon combustion several difficulties were encountered in the determination of aldehydes owing to interference from some of the other products of the reaction. The standard method using hydroxylamine hydrochloride, although giving accurate results with pure samples, is not specific for aldehydes but determines ketones also.

Peroxides cause serious interference and, in agreement with Smith and Mitchell (*Analyt. Chem.*, 1950, **22**, 750), we have found that the discrepancy amounts to between two and four times the amount of peroxide present, depending upon the temperature and time of standing. In addition weak acids, if present in quantity comparable with that of the aldehydes, lead to uncertain results owing to their buffering action.

A modification of Ripper's bisulphite method described by Siggia and Maxcy (*Ind. Eng. Chem., Anal.*, 1947, **19**, 1023) has also been tried. Although hydrogen peroxide does not interfere when in small concentration, tertiary butyl hydroperoxide liberates approximately one molecule of alkali for every two of peroxide present and so leads to high results.

When analysing combustion products we have found that a method based on the oxidising action of silver oxide on aldehydes is more satisfactory. Aldehydes are thus oxidised to fatty acids which then dissolve more oxide to form salts, the silver in which may readily be determined by titration with potassium thiocyanate. Smith and Mitchell (*Analyt. Chem.*, 1950, **22**, 746) have recently described a method similar to ours in which the aldehydes are heated to 60° with silver oxide in a stoppered flask; standard sodium hydroxide is added to precipitate the silver and the excess is back-titrated with hydrochloric acid. This method, however, suffers from the disadvantage that acetaldehyde and formaldehyde are only partially estimated. The method described below has been tested with these aldehydes amongst others and gives results which are accurate to within 2% for straight-chain saturated aliphatic aldehydes up to hexanoic. Not only is the silver oxide method of use for aldehydes where other methods may fail owing to interference, but it can also be made a basis for the quantitative separation and determination of individual aldehydes in mixtures. The fatty acids can be prepared from the silver salts and then separated by chromatography whereas there is no simple method of analysing a mixture of aldehydes as such.

Experimental.

Determinations.—The product to be analysed is made up to a standard volume either with water or, if insoluble in water, with 50% aqueous *iso*propyl alcohol. Between 1 and 5 ml. of this solution, containing about 0·2 millimoles of aldehyde, is allowed to pass down a tube of 8-mm. bore, packed with silver oxide to a depth of 10 cm. The sample is washed through with water to make a total volume of 25 ml. and the emergent solution containing the silver salts of the fatty acids is titrated with *N*/50-potassium thiocyanate, with ferric alum in nitric acid as indicator. A small correction (0·15 ml. for every 10 ml. of solution) must be made for the oxide dissolved by the wash-water.

When not in use the column is kept immersed in distilled water to prevent the oxide from drying out. The column described is easily overloaded and if amounts of aldehyde in excess of 0·2 millimoles are used a low result may be obtained. Care must also be taken, especially when dealing with higher aldehydes, to ensure that the silver salts are completely washed out, as their solubility decreases markedly with ascent of the homologous series. This may in some cases necessitate the use of more than 25 ml. of wash-water.

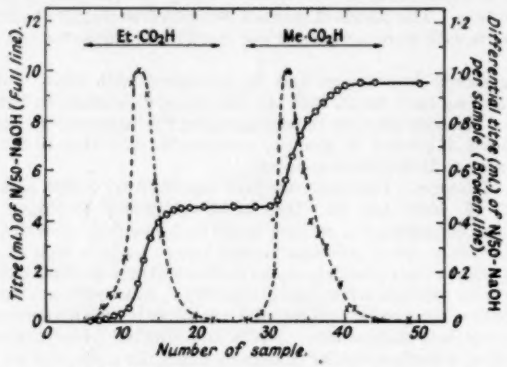
The method has been tested for formaldehyde, acetaldehyde, propaldehyde, *n*-butaldehyde, and hexanal. Solutions of each were standardised by hydroxylamine hydrochloride. The results by the two methods, for polymer-free aldehydes, agreed to within 2%.

Aldehyde determinations have also been carried out in the presence of hydrogen peroxide, *tert.*-butyl hydroperoxide, acetone, dimethyl formal, ethyl acetate, and alcohols. None of these substances caused

interference. Methyl and ethyl formate, however, are about 30% hydrolysed on a 10-cm. column and the formic acid liberated leads to a high result. Acids present in the original mixture dissolve silver oxide and must be allowed for.

Separation of Aldehydes.—The silver salt solution obtained from the oxide column is collected in a 30-ml. long-necked flask, treated with excess of sodium chloride to precipitate all the silver, and evaporated to dryness on a water-bath. The addition of sodium chloride is necessary since the silver salts readily decompose when heated. The free acids can then be obtained by Elsden's method (*Biochem. J.*, 1946, **40**, 252). The residue is treated with 0·2 ml. of water followed by enough powdered anhydrous potassium hydrogen sulphate to form a paste. This liberates the acids which are extracted with six 0·5-ml. portions of chloroform containing 1% of butanol. The acids in this solution are separated by partition chromatography on a suitably buffered silica column by the method of Moyle, Baldwin, and Scarisbrick (*ibid.*, 1948, **43**, 308) whereby the acids are titrated with alkali as they emerge from the column. Formaldehyde cannot be determined chromatographically by this method as it is very strongly adsorbed by the silica. It does not, however, interfere with the separation of the other acids.

The Figure shows the result of a separation which was carried out on a mixture of formaldehyde, acetaldehyde, and propaldehyde. Three separate solutions, each containing one of the aldehydes, were standardized by hydroxylamine hydrochloride. Equal amounts were then mixed and 3 ml. of the



mixture were used for the experiment. The sample was treated as outlined above, a column buffered to pH 6·0 being used for chromatography. The following figures show that 97% yields of acetaldehyde and propaldehyde were obtained. The titres are in ml. of N/50-solution.

	C_2H_5·CHO	CH_3·CHO	CH_2O
Amount as detd. by hydroxylamine HCl (ml.)	4·80	5·15	11·28
Amount as detd. by oxidn. and chromatography (ml.) ...	4·65	5·00	—
Yield, %	97	97	—

Propionic acid which travels fastest was eluted with chloroform containing 1% of butanol, and acetic acid with a 10% solution. Formic acid is retained by the column and has no effect on determination of the other two. It must be determined by difference or by an independent method.

A similar separation has been carried out on a mixture of butaldehyde and hexanal. The overall yields were : hexanal 95%, butaldehyde 96%. In this case a column buffered to pH 8·2 was used, and the two acids eluted with 1% and 30% solutions of butanol in chloroform respectively.

The above technique has been used successfully to identify and determine the amounts of different aldehydes in the combustion products of higher hydrocarbons. An account of this work will be published later.

Our grateful thanks are due to Professor R. G. W. Norrish for his help and encouragement. We are also indebted to the Distillers' Company Ltd., under whose auspices one of us is working (H. C. B.), and to the Carnegie Trust for the Universities of Scotland for a scholarship granted to the other (J. H. K.).

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610. *The Possibility of Geometrical Isomerism among the 1-Aryl-3 : 3-dimethyltriazens.*

By Raymond J. W. Le Fèvre and Thomas H. Liddicoet.

The dipole moments and ultra-violet absorption spectra of about a dozen 1-aryl-3 : 3-dimethyltriazens have been determined. The known forms of these substances appear to possess *trans*-configurations about the $-N{=}N-$ group. The mesomeric polarisations run parallel to those noted in the literature for dimethylaniline and its derivatives. Exposure to sunlight causes mainly photodecomposition but, beneath the dielectric constant and spectrometric evidence of this, slight indications are observable which resemble phenomena shown by other azo-derivatives and which would not be inconsistent with the occurrence of a reversible *trans* $\rightleftharpoons$ *cis* change.

According to Hantzsch's views regarding the stereostructure of the azo-group, *cis–trans*-isomers should exist among the diazo-carboxyamides ($R{\cdot}N{:}N{\cdot}CO{\cdot}NH_2$), the triazens ($R{\cdot}N{:}N{\cdot}NHR$ and $R{\cdot}N{:}N{\cdot}NR_2$), the diazosulphones ($R{\cdot}N{:}N{\cdot}SO_2{\cdot}R$), the diazo-ethers ($R{\cdot}N{:}N{\cdot}OR$), the diazo-sulphides ($R{\cdot}N{:}N{\cdot}SR$), etc. Despite past efforts to demonstrate such isomerism, the general conclusion seems to have been that known representatives of these classes occur only as single forms (see below; also Saunders, " The Aromatic Diazo-compounds and Their Technical Applications," 2nd Edn., E. Arnold & Co., London, 1949, pp. 139, 192, 387, 391). However, recently (*J.*, 1951, 1977) new evidence has been produced which indicates that certain diazo-carboxyamides do in fact undergo geometrical inversion under the action of light, and that the process is reversed in the dark.

We now report an examination of the aryldimethyltriazens recorded in Tables I and II.

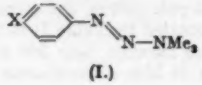
Table I.

Polarisations at infinite dilution in benzene at 25°, and apparent dipole moments of 1-aryl-3 : 3-dimethyltriazens.

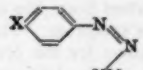
Ar in $Ar{\cdot}N{:}N{\cdot}NMe_2$	M_1	α_2	β	${}_TP_\infty$ (c.c.)	R (c.c.)	μ, D
C_6H_5	149·1	4·14	0·135	160	53	2·2$_8$
o-$Cl{\cdot}C_6H_4$	183·6	5·14	0·254	224	58	2·8$_5$
m-$Cl{\cdot}C_6H_4$	183·6	7·54	0·190	311	58	3·5$_8$
p-$Cl{\cdot}C_6H_4$	183·6	9·86	0·259	387	58	4·0$_1$
p-$Br{\cdot}C_6H_4$	228·0	7·57	0·379	373	60	3·9$_1$
o-$NO_2{\cdot}C_6H_4$	194·1	10·9$_5$	0·355	442	62	4·3$_1$
m-$NO_2{\cdot}C_6H_4$	194·1	18·8	0·223	738	59	5·76
p-$NO_2{\cdot}C_6H_4$	194·1	28·1	0·262	1075	59	7·0$_4$
p-$Me{\cdot}C_6H_4$	163·1	2·75	0·092	135	57	1·9$_5$
p-$MeO{\cdot}C_6H_4$	179·1	3·53	0·205	167	59	2·3$_0$
o-$C_6H_5{\cdot}C_6H_4$	225·1	2·99	0·191	189	79	2·3$_3$
p-$C_6H_5{\cdot}C_6H_4$	225·1	3·75	0·215	219	79	2·6$_1$
β-$C_{10}H_7$	199·1	3·63	0·249	187	71	2·3$_9$

Dissolved in benzene, these substances seem to suffer a slow photo-decomposition when exposed to sunlight—a conclusion supported both by dielectric constant and spectrometric determinations (see Experimental). From Table IV it will be noted that the dielectric constant is not always raised by irradiation, *e.g.*, with the *o*- and the *p*-nitrophenyl derivative decreases of *ca.* 0·01 unit occur. Subsequent storage in the dark tends to cause either no significant change or a further increase of ε; the *m*-nitrophenyltriazen is an exception in that darkness slightly over-compensates the initial alteration of dielectric constant. With the *o*- and *m*-nitrophenyl compounds there are also indications that re-irradiation of the " restored " (3rd Col., Table IV) solutions has, in smaller measure, qualitatively the same effect as with a fresh solution.

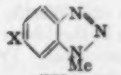
The data of Table IV would be understandable if irreversible destruction of solute were in varying degrees accompanied by reversible formation of a *cis*-isomer, *i.e.*, (I) $\rightleftharpoons$ (II). Unfortunately neither the relative polarities of (I) and (II) nor the directions of action of their



(I.)



(II.)



(III.)

molecular resultants can be forecast with certainty. When X = H the moment of (II) should approach the magnitude of that of benzotriazole ($\mu = 4{\cdot}07$ D.; Jensen and Friediger, *Kgl. Danske Vidensk. Selsk.*, **1943**, **20**, No. 20) or, more relevantly, that of the *N*-methyl derivative (III) ($\mu = 4{\cdot}16$ D., present work). A rise in moment, and hence in ε_{12}, during the transformation of (I) into (II) therefore seems likely. With other groups in various positions predictions of μ_I and μ_{II} are impossible on present knowledge.

In the preceding remarks we have assumed that as prepared these triazens have the *trans*-configuration (I). Table I lists the apparent dipole moments calculable from measurements taken before exposure to sunlight.

It is clear that, for a range of groups X, only forms extended as (I) should be smoothly related by polarity to the corresponding substituted dimethylanilines. Since no values for *o*- and *m*-derivatives of dimethylaniline have been reported to date (Marsden and Sutton, *J.*, 1936, 599) we quote also values for the appropriate anilines (cf. Wesson, M.I.T. Tables, 1948):

Substituent	H	*p*-Me	*o*-Cl	*m*-Cl	*p*-Cl	*p*-Br	*o*-NO_2	*m*-NO_2	*p*-NO_2
$C_6H_5{\cdot}N{:}N{\cdot}NMe_2$	2·3	1·9$_5$	2·8$_5$	3·5	4·0	3·9	4·3	5·8	7·0
$C_6H_5{\cdot}NMe_2$	1·6	1·3	—	—	3·3	3·4	—	—	6·9
$C_6H_5{\cdot}NH_2$	1·5	1·3	1·8	2·7	3·3	3·9	4·3	5·0	6·3

A satisfactory parallelism is noted, the moments of the triazens surpassing those of the amines in all cases except when an *o*-nitro-group is present. It is evident that the $-N_2{\cdot}NMe_2$ fragment carries a component moment whose negative pole is towards the aryl nucleus and that mesomeric polarisations of the type shown in (IV) are also operative. The differences between the moments of derivative and of parent are roughly the same in the triazen as in the aniline series. The exceptional *o*-nitro-products have structures such that mesomerism will be sterically inhibited (compare Remington, *J. Amer. Chem. Soc.*, **1945**, **67**, 1838). As information on the last point might be available from the ultra-violet spectra the prominent features of these are listed (Table II).

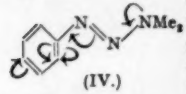

(IV.)

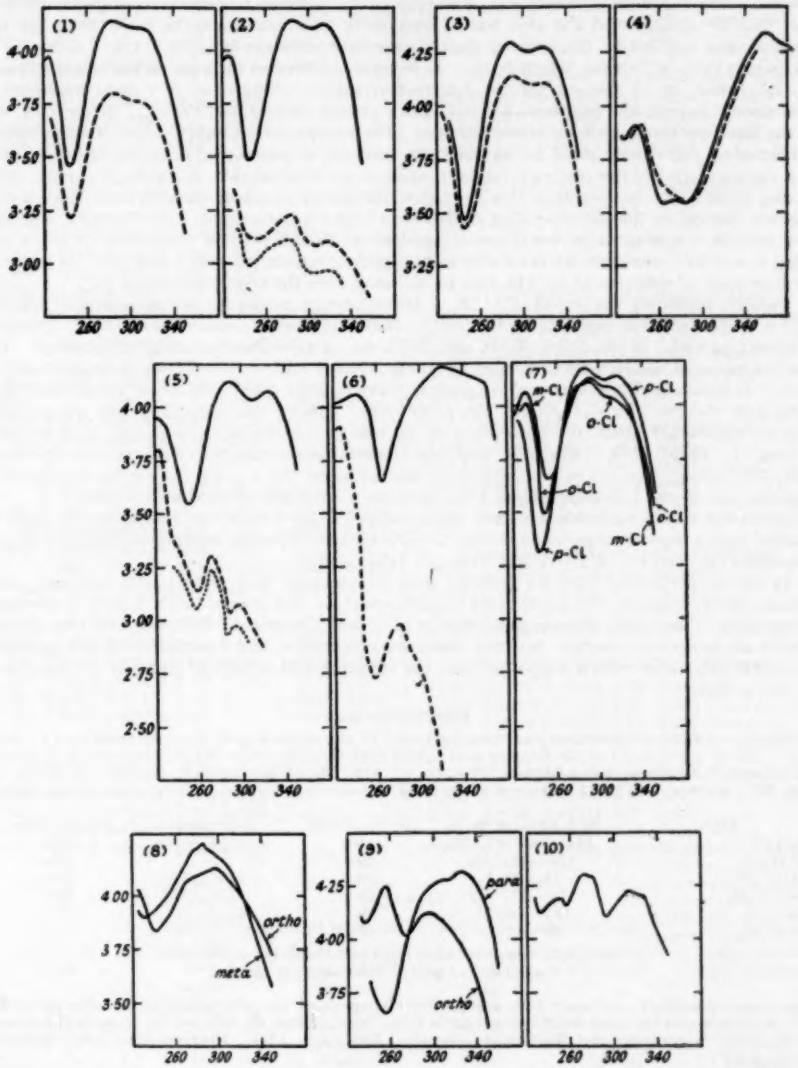
TABLE II.

Absorption maxima and inflexions.

Ar in Ar·N:N·NMe_2	$\lambda_{max.}$ ($\log_{10}\varepsilon_{max.}$)		
C_6H_5	225 (3·97)	285 (4·14)	308 (4·11) *
p-Me·C_6H_4	225 (3·98)	285 (4·15)	313 (4·13)
p-Br·C_6H_4	<230 (>3·93)	291 (4·29)	320 (4·27)
p-MeO·C_6H_4	*ca.* 222 (3·95)	288 (4·12)	324 (4·07)
o-$CO_2H{\cdot}C_6H_4$	240 (4·06)	—	{320 (4·19) {338 (4·13) *
o-Cl·C_6H_4	232 (4·02)	{281 (4·10) * {289 (4·12)	311 (4·04) *
m-Cl·C_6H_4	232 (4·07)	{285 (4·11) * {292 (4·13)	309 (4·09) *
p-Cl·C_6H_4	<224 (>3·94)	287 (4·18)	314 (4·15)
o-$NO_2{\cdot}C_6H_4$	<224 (>4·03)	*ca.* 280 (4·10) *	295 (4·13)
m-$NO_2{\cdot}C_6H_4$	<225 (>3·92)	{277 (4·22) * {286 (4·25) {290 (4·23) *	300 (4·18) *
p-$NO_2{\cdot}C_6H_4$	240 (3·90)	275 (3·55)	360 (4·33)
o-$C_6H_5{\cdot}C_6H_4$	<232 (>4·10) 255 (4·25)	292 (4·12) —	299 (4·12) *
p-$C_6H_5{\cdot}C_6H_4$	<240 (>3·81)	—	{*ca.* 305 (4·27) * {*ca.* 325 (4·31)
β-$C_{10}H_7$	<226 (>4·20)	252 (4·19) {*ca.* 272 (4·31) 280 (4·29) *	315 (4·23)

* Inflexion.

In general, aromatic azo-compounds absorb in three regions: below 250, from 300 to 350, and above 400 mμ. (cf. Cook, Jones, and Polya, *J.*, 1939, 1315; Winkel and Siebert, *Ber.*, 1941, **74**, 675; Le Fèvre and Wilson, *J.*, 1949, 1106; Freeman and Le Fèvre, *J.*, 1951, 415; Le Fèvre and Worth, *ibid.*, 1814). When pure, the triazens are all pale yellow, corresponding to bands in the blue end of the visible spectrum. The situation revealed by Table II is therefore unexceptional. Precedents are known for the occurrence of *two* maxima near 300 mμ., *e.g.*, the nitrobenzenediazocyanides (*J.*, 1949, 1106) are analogous to the nitro-triazens in this



Curve.	1-*Substituent.*	*Concn.,* (*mol./l.*) × 10^6.	*Curve.*	1-*Substituent.*	*Concn.,* (*mol./l.*) × 10^6.
1	Ph	102	7	*m*-Cl·C_6H_4	98·4
2	*p*-Me·C_6H_4	76·2	7	*p*-Cl·C_6H_4	100
3	*p*-Br·C_6H_4	87·3	8	*o*-NO_2·C_6H_4	59·6
4	*p*-NO_2·C_6H_4	99	8	*m*-NO_2·C_6H_4	81·4
5	*p*-MeO·C_6H_4	100	9	*o*-Ph·C_6H_4	97
6	*o*-CO_2H·C_6H_4	88·4	9	*p*-Ph·C_6H_4	112
7	*o*-Cl·C_6H_4	105	10	β-$C_{10}H_7$	92·4

——— *Original.* — — — — *After 4 hours' exposure.*
- - - - - - - *Exposed solution after 24 hrs. in darkness.*

respect. The " *K*-bands " (with $\log_{10} \varepsilon$ usually *ca.* 4), ascribed to general conjugation between the $-N{=}N-$ system and the aryl nuclei, commonly lie at wave-lengths *longer* than 300 mμ. Such a view applied to the present data makes interpretation possible: the " *K*-band " in the parent $C_6H_5{\cdot}N{:}N{\cdot}NMe_2$ is at 300 mμ.; as resonance increases through various *p*-substituents the $\lambda_{max.}$ rises, up to 360 mμ. for the *p*-nitro-derivative; where there is " steric inhibition of resonance," as with the *o*-chloro-, *o*-nitro-, and *o*-phenyl derivatives, the $\lambda_{max.}$ drops back, and in the last two instances falls below 300 mμ. The results for $o\text{-}CO_2H{\cdot}C_6H_4{\cdot}N{:}N{\cdot}NMe_2$ appear abnormal on this simple steric basis; they can however be understood if, owing to the presence of a carboxyl group, the molecule tends to exist as an internal salt, Burawoy (*J.*, 1937, 1865) having shown that the addition of a hydrogen nucleus to an azo-*K*-chromophore has a strong effect in displacing the corresponding *K*-bands to longer wave-lengths. Incidentally, Burawoy also records a spectrum of benzeneazopiperidine in hexane with a maximum at 289·5 mμ. ($\log_{10} \varepsilon = 4{\cdot}20$); the form of the curve is not quite symmetrical and could well be covering a minor peak or inflexion at *ca.* 310 mμ., in harmony with the triazens of Table II.

Finally, regarding the use of (III; X = H) as a rough model for the unknown *cis*-triazens (II), it is relevant that Macbeth and Price (*J.*, 1936, 111) found 1-methylbenzo-1 : 2 : 3-triazole to absorb at 258·5 (3·79), 279·5 (3·59), and 291·5 mμ. (3·45)—the last being an inflexion. The two longer-wave bands were associated by these authors with the Ar·N:N·N arrangement, *i.e.*, were " *K*-bands." They occurred at shorter wave-lengths (and with lower intensities) than those now observed for $C_6H_5{\cdot}N{:}N{\cdot}NMe_2$ (Table II). Among azo-derivatives the change *trans* ⟶ *cis* commonly alters the absorption at *ca.* 300 mμ. in the same sense (cf. Le Fèvre and Wilson, *J.*, 1949, 1106). The fact that the double maximum (285, 308 mμ.) observed for $C_6H_5{\cdot}N{:}N{\cdot}NMe_2$ (curve 1) is not detectably shifted along the λ scale by irradiation therefore suggests—as do the ε changes (Table IV)—that the *cis*-content so produced is small.

From the above evidence we draw the conclusions set out in the summary. It may be recalled that a *trans*-configuration of the $-N{=}N-$ unit was likewise inferred for the diazoaminobenzenes examined by Le Fèvre and Vine (*J.*, 1937, 1805).

In the Experimental part we describe tests which show that, even in dry benzene, these triazens slowly interact with β-naphthol to yield azo-dyes, the process being slightly accelerated by sunlight. Previously Hauser and Breslow (*J. Amer. Chem. Soc.*, 1941, **63**, 418) had demonstrated an analogous reaction between benzeneazopiperidine and β-naphthol in dry pyridine, a medium the use of which suggested that the coupling was unusually difficult (cf. Saunders, *op. cit.*, p. 224).

Experimental.

Solutes.—All the triazens used have been prepared by the method given by Elks and Hey (*J.*, 1943, 441). The m. p.s or b. p.s of the samples used agreed with those recorded in the literature (cf. Beilstein, " Handbuch " der Organischen Chemie," Vol. 16, pp. 686, 705; Elks and Hey, *loc. cit.*; Johnson, *J.*, 1946, 898; Hunter, *J.*, 1937, 324) except in the cases of those recorded in the Table, which do not appear

Aryl	B. p./mm. or m. p.	N, %, Found	Formula	N, %, Calc.
$p\text{-}C_6H_4Cl$	164—166°/27—28	23·2	$C_8H_{10}N_2Cl$	22·9
$m\text{-}C_6H_4Cl$	148—151°/20	22·6	,,	22·9
$o\text{-}NO_2{\cdot}C_6H_4$	31—32° *	29·0	$C_8H_{10}O_2N_4$	28·9
$p\text{-}OMe{\cdot}C_6H_4$	174—177°/29	23·4	$C_9H_{12}ON_2$	23·5
$o\text{-}Ph{\cdot}C_6H_4$	143—145°/1	18·4	$C_{14}H_{14}N_2$	18·7
$p\text{-}Ph{\cdot}C_6H_{14}$	70—71° †	18·85	,,	18·7

* Pale yellows prisms from light petroleum (b. p. 60—90°).
† Buff-coloured plates from aqueous alcohol.

to have been described previously and, unless otherwise specified, are pale yellow oils. 1-Methylbenzo-1 : 2 : 3-triazole was obtained from benzotriazole (*Org. Synth.*, 1940, **20**, 16), by use of methyl sulphate (Krollpfeiffer, Rosenberg, and Mülhausen, *Annalen*, 1934, **515**, 124). Recrystallised from ligroin it had m. p. 64°.

Dipole-moment Measurements.—These were made at 25°, with sodium-dried " crystallisable " benzene as solvent, with the apparatus and procedures noted before (*J.*, 1948, 1949; 1949, 333; *re* symbols cf. *Trans. Faraday Soc.*, 1950, **46**, 1, and *J.*, 1937, 1805). Details are set out, under the usual headings, in Table III. Refractivities have been directly determined in only three cases. Values shown in parentheses are derived from the figure obtained for the *p*-tolyl derivative, namely, 57·4 c.c., by noting that—since $R_{Toluene} = 31{\cdot}1$ and $R_H = 1{\cdot}1$—the group $Me_2N{\cdot}N{:}N-$ evidently contributes 27·4 c.c., so that the addition of 26·3 to the molecular refractions of benzene (26·2 c.c.), nitrobenzene (32·7 c.c.), chlorobenzene (31·4 c.c.), bromobenzene (34·0 c.c.), anisole (33·0 c.c.), diphenyl (52·4 c.c.), and naphthalene (44·5 c.c.) should give satisfactory estimates. As a check the $R_{calc.}$ for $C_6H_5{\cdot}N{:}N{\cdot}NMe_2$, *viz.*, 52·5 c.c. may be compared with that (52·7 c.c.) obtained from $R_{azobenzene} = 63{\cdot}7$ c.c. (Auwers, *Ber.*, 1938, **71**, 611), $R_H = 1{\cdot}1$ c.c., $R_{C_6H_5} = 26{\cdot}2$ c.c., and $R_{Me_2NH} = 15{\cdot}2$ (Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374). For the purposes of Table I, *R* has been taken to the nearest whole number in each case.

TABLE III.

10^6w_1	ε_{12}	d_{12}	αE_2	β	n_{12}	$[R_L]_D$	
0	2·2725	0·87378	—	—	$1·4972_5$	—	
3 : 3-*Dimethyl*-1-*phenyltriazen.*							
7,465	—	0·87476	—	0·150	—		
7,816	2·3049	—	4·14	—	—		
12,370	2·3243	0·87525	4·19	0·136	—		
15,020	2·3344	0·87535	4·12	0·120	—		
19,340	2·3521	0·87603	4·12	0·133	—		(52·5)
1-m-*Chlorophenyl*-3 : 3-*dimethyltriazen.*							
6,196	2·3180	0·87459	7·34	0·150	—		
14,067	2·3830	0·87572	7·85	0·158	—		
20,026	2·4250	0·87737	7·61	0·205	—		
26,789	2·4694	0·87954	7·35	0·246	—		(57·7)
1-p-*Bromophenyl*-3 : 3-*dimethyltriazen.*							
6,006	2·3191	0·87569	7·76	0·364	—		
9,194	2·3422	0·87718	7·58	0·423	—		
12,515	—	0·87761	—	0·350	—		
14,146	2·3762	0·87851	7·33	0·383	—		
18,597	2·4131	0·87989	7·56	0·376	—		
21,451	2·4362	0·88091	7·63	0·380	—		(60·3)
3 : 3-*Dimethyl*-1-m-*nitrophenyltriazen.*							
5,452	2·3754	0·87478	18·9	0·210	1·4975	56·3	
7,316	2·4083	0·87515	18·6	0·214	1·4979	60·8	
8,022	2·4237	0·87534	18·9	0·223	—	—	
11,591	2·4908	0·87628	18·8	0·247	1·4985	61·0	
Mean $[R_L]_D$ = 59·4 c.c., calc. = 59·0 c.c.							
3 : 3-*Dimethyl*-1-p-*tolyltriazen.*							
3,842	2·2836	0·87408	2·89	0·089	—	—	
6,698	2·2916	0·87412	2·85	0·058	1·4978	59·4	
9,795	2·2976	0·87465	2·56	0·102	—	—	
10,360	2·3003	0·87467	2·69	0·098	1·4983	58·2	
20,140	2·3276	0·87574	2·74	0·111	1·4989	55·4	
Mean $[R_L]_D$ = 57·4 c.c.							
1-o-*Diphenylyl*-3 : 3-*dimethyltriazen.*							
2,878	2·2810	0·87426	$2·94_5$	0·191	—		
3,010	2·2811	0·87427	2·86	0·186	—		
5,254	2·2883	0·87466	3·02	0·192	—		
6,491	2·2928	0·87488	3·13	0·193	—		(78·7)
1-o-*Chlorophenyl*-3 : 3-*dimethyltriazen.*							
5,692	2·2917	0·87502	5·13	0·249	—		
11,733	2·3347	0·87673	5·30	0·288	—		
15,189	2·3486	0·87709	5·01	0·244	—		
20,471	2·3772	0·87802	5·12	0·237	—		(57·7)
1-p-*Chlorophenyl*-3 : 3-*dimethyltriazen.*							
4,363	2·3158	0·87492	9·92	0·299	—		
8,297	2·3543	0·87552	9·86	0·240	—	—	
11,160	2·3824	0·87627	9·85	0·255	—		
17,000	2·4391	0·87741	9·80	0·244	—		(57·7)
3 : 3-*Dimethyl*-1-o-*nitrophenyltriazen.*							
3,664	2·3113	0·87488	10·6	0·344	1·4974	60·6	
4,309	2·3196	0·87506	10·9	0·330	—	—	
6,400	2·3452	0·87577	11·4	0·356	1·4984	61·5	
7,685	2·3561	0·87633	10·9	0·380	1·4989	64·0	
Mean $[R_L]_D$ = 62·0 c.c., calc. = 59·0 c.c.							
3:3-*Dimethyl*-1-p-*nitrophenyltriazen.*							
2,570	2·3408	0·87440	26·6	0·276	—		
3,015	2·3584	0·87452	28·5	0·281	—		
4,036	2·3887	0·87488	28·8	0·312	—		
4,856	2·4091	0·87489	28·1	0·273	—		
6,404	2·4535	0·87472	28·3	0·168	—		(59·0)
1-p-*Methoxyphenyl*-3 : 3-*dimethyltriazen.*							
4,979	2·2900	0·87467	3·52	0·205	—		
7,979	2·3014	0·87531	3·62	0·219	—		
8,851	2·3038	0·87537	3·54	0·206	—		
17,728	2·3333	0·87672	3·43	0·190	—		(59·3)
1-p-*Diphenylyl*-3 : 3-*dimethyltriazen.*							
14,35	2·2779	0·87405	3·76	0·215	—		
5,209	2·2926	0·87478	3·86	0·220	—		
6,874	2·2976	0·87507	3·65	0·215	—		
8,784	2·3052	0·87538	3·72	0·209	—		(78·7)
3 : 3-*Dimethyl*-β-*naphthyl*-1-*triazen.*							
3,868	2·2866	0·87467	3·65	0·263	—		
6,134	2·2950	0·87515	3·67	0·256	—		
7,453	2·2995	0·87531	3·62	0·235	—		
10,977	2·3118	0·87609	3·58	0·241)	—		(70·8)

TABLE IV.

*Changes of ε through successive illumination and darkness.**

1-Substituent	Initial ε^{25}	After 4 hrs'. daylight	After 20—24 hrs'. darkness	After 4 hrs'. daylight	After 20—24 hrs'. darkness
Ph	2·3521	2·355	2·362	—	—
o-Cl·C_6H_4	2·3486	2·352	2·356	—	—
p-Br·C_6H_4	2·3422	2·347	2·355	—	—
o-NO_2·C_6H_4	2·3561	2·345	2·354	2·351	—
m-NO_2·C_6H_4	2·4908	2·501	2·487	2·490	2·494
p-NO_2·C_6H_4	2·4091	2·394	2·414	—	—
p-Me·C_6H_4	2·3276	2·328	2·328	—	—
p-MeO·C_6H_4	2·3014	2·319	2·318	—	—
p-Ph·C_6H_4	2·3052	2·306	2·305	—	—

* Concns. may be identified *via* ε values in Table III.

Effect of Sunlight on the Dielectric Constants of the Above Solutions.—The ε^{25} values of Table III were obtained on solutions freshly made up in brown bottles. After the initial capacity determinations, the solutions were transferred to clear-glass flasks, exposed to sunlight for 4 hours, and then remeasured. Subsequently, after 20—24 hours' storage in the dark, they were examined again. In the case of the *m*-nitrophenyl derivative, the "light–dark" cycle was performed twice. Sample observations are recorded in Table IV.

Interactions of the Triazens with β-Naphthol.—To β-naphthol (0·5 g.) in benzene (10 c.c. of the solvent used for dipole moment determinations), approx. 0·002 mole of the triazen was added. The mixtures were divided into two portions, one kept in the dark and the other exposed to bright sunlight. Inspections at hourly intervals indicated that illumination accelerated the production of colour. This was particularly noticeable with the *p*-chloro-, *p*-bromo-, *p*-methyl-, and *p*-methoxy-derivatives, and less so with the others.

In view of the possibility (Le Fèvre and Northcott, *Chem. and Ind.*, 1948, 543) that β-naphthol might considerably screen off from the dissolved triazen the wave-band around 300 mμ., three experiments were made, as checks, in which the triazen–benzene mixture was irradiated alone and the naphthol solution added only at the moment of test. However, this alternative procedure did not cause significantly different results.

By partial evaporation of five of these triazen–β-naphthol mixtures crystalline products were isolated. In colours and m. p.s these agreed with descriptions given in Beilstein (" Handbuch der Organischen Chemie," Vol. 16, pp. 162—170) for the expected azo-compounds, $HO{\cdot}C_{10}H_6{\cdot}N{:}N{\cdot}C_6H_4{\cdot}X$.

Group X	M. p. (observed)	M. p. (Beilstein)
H	132°	128·5°, 129·5°
		133, 134
p-Cl	155—157	158, 160
p-Br	171	172—173
p-CH_3	133—134	134—135
p-(OCH_3)	139—140	141

The recovered materials did not depress the m. p.s of appropriate authentic specimens.

Absorption Spectra.—These were determined with the Beckman photoelectric spectrophotometer, Model DU, in 95% ethanol as a solvent. Their forms are shown in the figures. Prominent features are listed in Table II.

The Dipole Moment of 1-*Methylbenzo*-1 : 2 : 3-*triazole.*—The necessary measurements (in benzene at 25°) are listed below, as under the first five headings used in Table III :

0	2·2725	0·87378	—	—
1253	2·2911	0·87409	14·8	0·283
2814	2·3131	0·87451	14·4	0·297
3554	2·3222	0·87484	14·0	0·298
5797	2·3553	0·87528	14·3	0·294

Since mean $\alpha\varepsilon_2 = 14{\cdot}4$ and mean $\beta = 0{\cdot}293$, ${}_{\infty}P_1 = 393$ c.c. The molecular refraction (D line) has already been determined in quinoline solution by von Auwers (*Ber.*, 1938, **71**, 604) as 38·23 c.c. Accordingly the apparent moment of 1-methyl-1 : 2 : 3-benztriazole is $4{\cdot}1_6$ D.

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611. *Synthetic Long-chain Aliphatic Compounds. Part V.** n-*Nonatricosanoic and* n-*Hexapentacosanoic Acids.*

By R. E. BOWMAN and R. G. MASON.

In continuation of attempts to ascend the homologous series of the straight-chain fatty acids, 18-ketononatricosanoic and 18-ketohexapentacosanoic acids † have been synthesised by our general method (Bowman, *J.*, 1950, 325) and have been reduced to the corresponding saturated acids.

IN Part II (*J.*, 1950, 174), we reported the synthesis of *n*-tricosanoic acid by using the ester (I; $n = 7$, R = Et) as a means of extending the chain :

$$(RO_2C)_2CH{\cdot}[CH_2]_n{\cdot}CO_2R \xrightarrow[3CH_2Ph{\cdot}OH]{Na-} (CH_2Ph{\cdot}O_2C)_2CNa{\cdot}[CH_2]_n{\cdot}CO_2{\cdot}CH_2Ph$$

(I.)

$$\xrightarrow[(b)\ H_2\text{-}Pd;\ (c)\ -2CO_2]{(a)\ R'COCl\ (III.);} R'CO{\cdot}[CH_2]_{n+1}{\cdot}CO_2H \longrightarrow R'{\cdot}[CH_2]_{n+2}{\cdot}CO_2H$$

(IV.) (V.)

As it was clearly desirable to use a longer molecule for this purpose, we chose methyl hexadecane-1 : 1 : 16-tricarboxylate (I; $n = 15$, R = Me), which was prepared by two different routes from readily available starting materials.

* Part IV, *J.*, 1951, 1087. † Geneva notation ($CO_2H = 1$) is used throughout.

First, diethyl hexadecane-1 : 16-dicarboxylate (VI) (Swann, Oehler, and Pinkney, *Org. Synth.*, 1941, **21**, 48) was treated with ethyl oxalate in the presence of sodium ethoxide by a modification of Floyd and Miller's method (*J. Amer. Chem. Soc.*, 1947, **69**, 2354), to give mainly the mono-oxalo-derivative (VII) which, without further purification, was thermally degraded to the crude triester (VIII); hydrolysis then yielded a product from which the pure tricarboxylic acid (IX) was obtained, and this was esterified with methanol to the crystalline ester (I; $n = 15$, R = Me); a significant amount of the corresponding tetracarboxylic acid (X) was also obtained.

$$EtO_2C\cdot[CH_2]_{15}\cdot CH_2\cdot CO_2Et \longrightarrow \underset{\text{(VI.)}}{EtO_2C\cdot[CH_2]_{15}\cdot CH(CO_2Et)\cdot CO\cdot CO_2Et} \longrightarrow \underset{\text{(VII.)}}{EtO_2C\cdot[CH_2]_{15}\cdot CH(CO_2Et)_2} \longrightarrow \underset{\text{(VIII.)}}{HO_2C\cdot[CH_2]_{15}\cdot CH(CO_2H)_2} \longrightarrow (I;\ n = 15,\ R = Me)$$

$$\underset{\text{(IX.)}}{(HO_2C)_2CH\cdot[CH_2]_{14}\cdot CH(CO_2H)_2} \quad \text{(X.)}$$

Alternatively, aleuritic acid (XI) was converted by Hunsdiecker's method (*Ber.*, 1943, **76**, *B*, 142) into the unsaturated acid (XII) which on catalytic hydrogenation and subsequent esterification furnished the ester (I; $n = 15$, R = Me) identical with the product obtained by the first route.

$$\underset{\text{(XI.)}}{HO\cdot[CH_2]_6\cdot CH(OH)\cdot CH(OH)\cdot[CH_2]_7\cdot CO_2H} \xrightarrow[\text{(b) Zn–MeOH}]{\text{(a) HBr–HAc}} Br\cdot[CH_2]_6\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2Me$$

$$\xrightarrow[\text{hydrolysis}]{\text{Malonation;}} \underset{\text{(XII.)}}{CH(CO_2H)_2\cdot[CH_2]_6\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H} \xrightarrow[\text{MeOH}]{H^+;} (I;\ n = 15,\ R = Me)$$

The ester (I; $n = 15$, R = Me) was used in preliminary experiments on the ascent of the series as follows. Purified behenic acid was converted by reaction with oxalyl chloride into its chloride (III; $R' = C_{21}H_{43}$), and this was treated with the tribenzyl sodio-derivative of (IX). Debenzylation and decarboxylation in the usual manner then furnished 18-ketononatricosanoic acid (IV; $n = 15$, $R' = C_{21}H_{43}$) in satisfactory yield and purity, and this was reduced by Huang-Minlon's method (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) to *n*-nonatricosanoic acid.

Repetition of the keto-acid synthesis, the C_{29} acid being used in place of behenic acid, gave crude 18-ketohexapentacosanoic acid (IV; $n = 15$, $R' = C_{25}H_{51}$) (m. p. 117—118°) in 86% yield, and after some difficulty (see p. 2751) this was purified and had m. p. 119·2—120·2°. On reduction (see p. 2751), this afforded *n*-hexapentacosanoic acid, $C_{25}H_{111}\cdot CO_2H$, in high yield.

We regard the foregoing work as exploratory in the handling of very long-chain compounds; and experiments are in progress to determine whether the rather wide melting-point ranges of the C_{34} derivatives are due to the length of chain or to impurity.

Experimental.

The methods of effecting the ketone synthesis were those already described (Bowman, *J.*, 1950, 325) except that the sodium ethoxide required for the preparation of the sodio-malonic esters was obtained by use of an aliquot portion of a standard solution of sodium ethoxide in pure absolute ethanol.

Ethyl Hexadecane-1 : 16-dicarboxylate (VI).—The ester was prepared according to the method described in *Org. Synth.* (*loc. cit.*) from potassium ethyl sebacate. The crude product, m. p. 41°, was separated by distillation *in vacuo* into two fractions, (*a*) b. p. 180°/1 mm., m. p. 46° (80%), and (*b*) b. p. 220°/1 mm., m. p. 64° (20%), consisting of substantially pure ethyl tetracosane-1 : 24-dicarboxylate. Fraction (*a*) was further purified by recrystallisation from light petroleum (b. p. 60—80°) to give material, m. p. 47° (constant). A sample of the latter was hydrolysed to the acid, m. p. 124·1° (lit., m. p. 124°), the solubility of which in acetone and ethylene dichloride at 20° was *ca.* 2% and 4%, respectively.

Hexadecane-1 : 1 : 16-tricarboxylic Acid (IX).—(*a*) Sodium (2·3 g., 0·1 mol.) was dissolved in dry ethanol (50 ml.) in a flask fitted with a short fractionating column suitable for use under reduced pressure, and the solution evaporated to dryness *in vacuo*. A solution of ethyl oxalate (14·6 g., 0·1 mol.) and ethyl hexadecane-1 : 16-dicarboxylate (38 g., 0·1 mol.) in toluene (200 ml.) was then added, and the mass kept at 45°/90 mm. for 12 hours, during which ethanol (3·7 g.), in the form of its azeotrope with toluene, was collected. The reaction mixture was then acidified at 0° with excess of hydrochloric acid, and the oxalo-derivatives extracted from the organic layer by shaking it with a solution of sodium hydroxide (2 g.) in water (125 ml.) and acetone (125 ml.) at 0°. The bulked acetone extracts were washed with fresh toluene and acidified at 0° in the presence of benzene (200 ml.). Evaporation of the

benzene solution furnished the crude oxalo-derivatives (24 g.), and the bulked toluene solutions afforded unchanged ethyl hexadecane-1 : 1 : 16-tricarboxylate (21 g.).

The oxalo-derivative was heated at 160—180° under 2 mm. pressure for 3 hours, giving 21 g. of crude residue, hydrolysis of which in the usual manner furnished an acid of m. p. 87—100° which was separated as follows. The crude product was dissolved in acetone (100 ml.), and the solution cooled to 10°, crude hexadecane-1 : 1 : 16-tricarboxylic acid, m. p. 117°, separating; dilution of the filtrate with an equal volume of water then precipitated the tricarboxylic acid, which was dissolved by heating and then allowed to cool, whereupon it (10·2 g.) separated: it had m. p. 90°. Evaporation of most of the acetone from the mother-liquor furnished crude hexadecane-1 : 1 : 16 : 16-tetracarboxylic acid (4 g.), which separated from aqueous acetone in clusters of prismatic needles, m. p. 138°, of the *hemihydrate* (Found : C, 58·2; H, 8·4. $C_{30}H_{54}O_8,\frac{1}{2}H_2O$ requires C, 58·4; H, 8·5%). Hexadecane-1 : 1 : 16-tricarboxylic acid was purified by crystallisation from aqueous acetone (5 vols. ; 1 : 1) and then from ethylene dichloride, from which it separated in colourless laths as the *monohydrate*, m. p. 90·5° (Found : C, 60·5; H, 9·6. $C_{19}H_{34}O_6.H_2O$ requires C, 60·6; H, 9·6%).

Both the tri- and the tetra-carboxylic acid, when heated to 180°, furnished hexadecane-1 : 16-dicarboxylic acid, m. p. 124°.

(*b*) Hexadec-9-ene-1 : 1 : 16-tricarboxylic acid (XII) was prepared from aleuritic acid (120 g.) according to Hunsdiecker's procedures (*loc. cit.*; see Bloomquist and Holley, *J. Amer. Chem. Soc.*, 1948, **70**, 36), except that the crude 15-bromopentadec-9-enoic acid, m. p. 38—40°, was esterified with methanol by the method of Brown *et al.* (*J. Org. Chem.*, 1947, **12**, 160) by using chloroform (200 ml.), methanol (150 ml.), and sulphuric acid (2 ml.) to give the methyl ester as a yellow oil, b. p. 162—164°/0·1 mm. (Hunsdiecker gives b. p. 179°/2 mm.), which was treated with sodio-malonic ester as described. The unsaturated tricarboxylic acid (XII) (30 g.; m. p. 69—70°) was dissolved in ethyl acetate (300 ml.) and hydrogenated at atmospheric pressure by use of palladised charcoal (3% Pd). After removal of the catalyst, cooling of the filtrate to −5° deposited pure hexadecane-1 : 1 : 16-tricarboxylic acid, m. p. 90° (30 g.).

Methyl n-*Hexadecane*-1 : 1 : 16-*tricarboxylate*.—The free acid, prepared by either method, was esterified by dissolution in 10 times its weight of 1% methanolic hydrogen chloride; the solution was kept at 40° for 12 hours and then evaporated to dryness under reduced pressure. Two repetitions of this process and crystallisation of the residue from methanol (5 vols.) at 10° furnished the pure *ester* (90%) as colourless plates, m. p. 45° (Found : C, 65·8; H, 10·2. $C_{22}H_{40}O_6$ requires C, 66·0; H, 10·0%).

18-*Ketononatricosanoic Acid*.—A sample of behenic acid, obtained by hydrogenation of purified erucic acid, was crystallised in turn from ethanol (3 times), acetone, ethyl acetate, benzene, and dioxan to give material of f. p. 79·5°, m. p. 79·8°. The acid (8·5 g., 0·025 mol.) was dissolved in dry benzene (75 ml.), excess of oxalyl chloride (6 g.) added dropwise, and the solution refluxed for 0·5 hour. Excess of oxalyl chloride was then removed by distillation through a short Fenske column until the distillate was free from halogen. The resulting solution of behenoyl chloride was then added to a benzene solution (250 ml.) of tribenzyl sodio-hexadecane-1 : 1 : 16-tricarboxylate prepared in the usual manner from the methyl ester (10 g., 0·025 mol.), benzyl alcohol (8·1 g., 0·075 mol.), and sodium ethoxide (0·025 mol. as 7% solution in ethanol), and the mixture set aside at room temperature for 24 hours. After being worked up as usual, the keto-triester (23·8 g.) was hydrogenated in ethyl acetate solution (200 ml.) in the presence of palladised strontium carbonate (4 g.; 10% Pd) until the required volume of hydrogen had been absorbed. The reaction mixture was then warmed to 40° to dissolve some solid matter which had separated during the hydrogenation, and filtered, and the catalyst extracted with boiling ethyl acetate (100 ml.). The combined ethyl acetate solutions were boiled under reflux for 0·5 hour to effect decarboxylation and then cooled to room temperature; 18-*ketononatricosanoic acid* (10·1 g., 70%), m. p. 110°, separated and was crystallised from boiling toluene (150 ml.) several times, forming microscopic rhombohedra (9·6 g.), m. p. 110·3—110·6° (Found : C, 78·8; H, 12·7. $C_{23}H_{76}O_3$ requires C, 79·1; H, 12·8%).

n-*Nonatricosanoic Acid*.—A mixture of the foregoing keto-acid (9·3 g.), potassium hydroxide (4 g.), hydrazine hydrate (5 ml.; 50%), and 2 : 2′-dihydroxydiethyl ether (100 ml.) was heated under reflux at 140° for 4 hours, whereafter the temperature of the mixture was raised to 200° by distillation and kept at that temperature for 7 hours. Water (10 ml.) was then added, and the solution refluxed for a further 3 hours. The cooled solution was diluted with water and acidified with excess of hydrochloric acid to give the almost pure acid, m. p. 101·2° (9 g., 99%). Crystallised to constant m. p. from toluene (3 × 150 ml.) and ethyl methyl ketone (3 × 200 ml.), the *acid* (8·4 g.) was obtained as microscopic plates, m. p. 101·3—102° (Found : C, 80·5; H, 13·2. $C_{23}H_{78}O_2$ requires C, 80·9; H, 13·5%).

A sample of the acid (0·5 g.) was treated with oxalyl chloride in benzene (10 ml.) at 50° for 4 hours, the solution evaporated to dryness, and the residual acid chloride refluxed with methanol (5 ml.) for 12 hours. Evaporation and crystallisation (4 times) from acetone–toluene furnished *methyl* n-*tricosanoate* as ill-defined plates, m. p. 82·1—82·5° (Found : C, 80·7; H, 13·3. $C_{40}H_{80}O_2$ requires C, 81·1; H, 13·5%).

18-*Ketohexapentacosanoic Acid*.—The foregoing acid (17·3 g.) was converted into its acid chloride with oxalyl chloride (10 g.) as previously described, and the product treated with tribenzyl sodio-hexadecane-1 : 1 : 16-tricarboxylate (0·033 mol.) as in the previous experiment. The resulting acylmalonic ester solidified on removal of solvent but dissolved in ethyl acetate (500 ml.) on warming to 50°. Palladised strontium carbonate (4 g.; 10% Pd) was added to the solution, which was then stirred in an atmosphere of hydrogen at 30°. Absorption of gas was slow after a rapid start probably because the product crystallised from the solution, coating the surface of the catalyst. Hydrogenation was carried out at 30° for 4 hours, then at 50° for a further 4 hours, whereafter no further gas absorption took place.

Removal of the solvent and decarboxylation was then effected by heating the mixture at 120° (oil-bath) until no further distillation took place. The residue was then boiled with toluene (2 × 500 ml.), and filtration carried out at the b. p. The combined filtrates, on cooling, deposited the crude keto-acid, which was filtered off and dried: the yield was 21·5 g. (86%), and the m. p. 117—118°. An attempted determination of its equivalent weight by titration in boiling aqueous 2 : 2′-dihydroxydiethyl ether with 0·1N-sodium hydroxide gave a value of 1670 (Calc.: 830), presumably owing to the separation of a highly insoluble sodium acid salt, $C_{38}H_{77}\cdot CO\cdot[CH_2]_{16}\cdot CO_2Na,C_{38}H_{77}\cdot CO\cdot[CH_2]_{16}\cdot CO_2H$. In alcoholic solution, lower values (*ca.* 1100) were obtained with difficulty.

The keto-acid was exceedingly insoluble in most of the common lower-boiling solvents but dissolved readily in boiling toluene and *cyclo*hexanone, separating on cooling in gelatinous form from which the high-boiling solvent was best removed by trituration with cold acetone and subsequent drying *in vacuo*. In attempts to purify this substance, a sample (5 g.) was dissolved in boiling toluene, the solution allowed to cool to $T°$, and the mixture filtered; the crop was dried as above, and its m. p. ($t_c°$) recorded. The filtrate was then evaporated to dryness under reduced pressure, and the residue weighed (w) and its m. p. ($t_r°$) taken:

No. of cryst.	Vol. of toluene, c.c.	T.	Crop: $t_c°$.	Residue: w (mg.).	$t_r°$.	No. of cryst.	Vol. of toluene, c.c.	T.	Crop: $t_c°$.	Residue: w (mg.).	$t_r°$.
1	110	19°	117°	28	89°	24	180	40°	119·4°	10	107°
2	110	15	117	2	89	27	180	55	119·7	190	119
6	160	18	117·3	22	93	28	190	55	119·7	200	119·5
11	240	35	118	250	96	29	160	53	119·7	100	119·7
15	200	37	118	90	99	30	200	30	119·7	trace	119·7

The m. p.s, t_c and t_r, were not as sharp, as indicated above, but represent the same stage of collapse in the capillary; it is perhaps significant that all the m. p.s of the C_{38} compounds were not nearly so sharp as those of the corresponding C_{39} materials. Guided by these results, we quickly purified the main bulk by crystallisation from boiling toluene, the acid separating at 50—55° being collected. n-18-*Keto-hexapentacosanoic acid* was thus obtained as microscopic plates, m. p. 119·2—120·2° (Found: C, 80·7; H, 13·0. $C_{38}H_{110}O_3$ requires C, 81·0; H, 13·2%). The *ethyl* ester, prepared by the azeotropic method and crystallised from toluene, had m. p. 95·6—96·1° (Found: C, 80·8; H, 13·1. $C_{40}H_{114}O_3$ requires C, 81·1; H, 13·3%).

Wolff–Kishner Reduction of 18-*Ketohexapentacosanoic Acid*.—(*a*) The first experiment was carried out as in the case of the C_{39} keto-acid by using the foregoing keto-acid (1 g.), hydrazine hydrate (1 ml.; 50%), potassium hydroxide (1 g.), and 2 : 2′-dihydroxydiethyl ether (35 ml.). The product, however, had m. p. 117°, raised to 118° by admixture with the original keto-acid and was, presumably, only partly reduced (Found: C, 80·5; H, 13·1%).

(*b*) After several such failures, it seemed likely that the main difficulty was due to the use of a quantity of hydrazine which, although large in proportion to the keto-acid, was nevertheless small enough to be volatilised into the empty space of the flask and condenser under the conditions of reflux. Accordingly, conditions were modified, and a large excess of the base was used as follows: A mixture of the keto-acid (1 g.), potassium hydroxide (1 g.), hydrazine hydrate (7 ml.; 50%), and 2 : 2′-dihydroxydiethyl ether (50 ml.) was heated at 125° (bath-temp.) for 24 hours, then slowly (2 hours) raised to 200°, and kept at that temperature for a further 5 hours. The reaction mixture, which was homogeneous at the start of the final stage, separated into two phases later. A sample of the top phase was decomposed by boiling it with dilute hydrochloric acid to give a material of m. p. 114—115°, which, however, when boiled for 72 hours with a mixture of concentrated hydrochloric acid (5 ml.), acetic acid (5 ml.), and toluene (10 ml.), was slowly decomposed, giving a product whose m. p. slowly fell to 110°. Decomposition of this product, which may be an acid hydrazide, may also be accomplished by alkaline hydrolysis, since addition of water (7 ml.) to the main bulk of reduction mixture, followed by refluxing for 24 hours and subsequent acidification in the usual manner, gave, in almost quantitative yield, the substance of m. p. 110°.

n-*Hexapentacosanoic acid*, obtained in this manner, was readily purified by crystallisation from toluene and had m. p. 109·3—109·6° (Found: C, 82·0; H, 13·5. $C_{38}H_{112}O_2$ requires C, 82·3; H, 13·7%). It formed an *ethyl* ester, which crystallised from toluene or dioxan, and had m. p. 99·3—100·2° (Found: C, 82·1; H, 13·5. $C_{40}H_{116}O_2$ requires C, 82·4; H, 13·7%).

We are indebted to the directors of Messrs. A. Boake Roberts and Co. Ltd. for facilities provided to one of us (R. G. M.) for carrying out much of the work described herein.

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612. *Synthetic Long-chain Aliphatic Compounds. Part VI.* Some Anomalous Reductions of 9-Keto-10-methoxyoctadecanoic Acid.†*

By D. E. Ames and R. E. Bowman.

In Part II of this series (Bowman, *J.*, 1950, 177) we examined the reduction of 13-keto-14-methoxydocosanoic acid † (I; $n = 11$) by sodium and alcohol and by zinc and acid, and the products were thought to be 13- (II; $n = 11$) and 14-hydroxydocosanoic (III; $n = 11$) acids, respectively. Confirmation of these conclusions was not possible, however, for both the

$$\begin{array}{c} CH_3\cdot[CH_2]_7\cdot CH(OMe)\cdot CO\cdot[CH_2]_n\cdot CO_2H \\ \text{(I.)} \\ \text{Na–EtOH} \qquad\qquad \text{Zn} \\ \text{(II.)}\ CH_3\cdot[CH_2]_6\cdot CH(OH)\cdot[CH_2]_n\cdot CO_2H \qquad CH_3\cdot[CH_2]_7\cdot CH(OH)\cdot[CH_2]_{n+1}\cdot CO_2H\ \text{(III.)} \end{array}$$

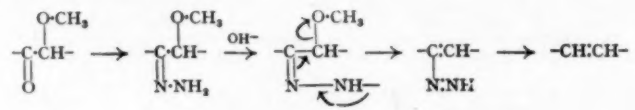
hydroxy-acids were new, and only one of the corresponding keto-acids was known. We have now examined similar reductions of the corresponding octadecanoic acid (I; $n = 7$) (Part III; *J.*, 1951, 1079) in the hope of confirming the above results, since both of the expected hydroxy-acids had been prepared previously.

With sodium and alcohol, the acid (I; $n = 7$) did, in fact, yield the expected hydroxy-acid (II; $n = 7$), identified by oxidation to the corresponding keto-acid. On the other hand, with zinc under Clemmensen conditions, a mixture of hydroxy-acids was obtained but reduction with zinc and hydrochloric–acetic acids yielded an apparently pure hydroxy-acid, m. p. 81—82°, oxidised to a keto-acid, m. p. 84°. This m. p. agrees with that previously reported for 10-keto-octadecanoic acid, but various m. p.s between 80° and 85° have been reported for the expected hydroxy-acid (III; $n = 7$); Tomecko and Adams (*J. Amer. Chem. Soc.*, 1927, **49**, 523) recorded m. p. 81—82° and Robinson and Robinson (*J.*, 1925, **127**, 175) gave m. p. 84·5°. There is still, therefore, some ambiguity regarding the reduction with zinc and this can only be resolved by synthesis.

We have also examined the reduction of the methyl ester of the acid (I; $n = 7$) by Huang-Minlon's modification (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) of the Wolff–Kishner method. As far as we are aware, no example of the reduction of an acyloin ether has been reported. Examples of the reduction of acyloins by the Wolff–Kishner method have been mainly confined to the sterol series (Barton, Holness, and Klyne, *J.*, 1949, 2456, and references cited therein) and have been shown to give the fully reduced compound (IV) or, in some cases, the corresponding unsaturated compound (V). Kishner (*J. Russ. Phys. Chem. Soc.*, 1913, **45**, 973) described the reduction of 2-hydroxy-3-keto-2 : 6-dimethyloctane to 2 : 6-dimethyloct-2-ene.

$$\begin{array}{ccc} R\cdot CH_2\cdot CH_2\cdot R' & \longleftarrow & R\cdot CH(OH)\cdot CO\cdot R' \longrightarrow R\cdot CH{:}CH\cdot R' \\ \text{(IV.)} & & \text{(V.)} \end{array}$$

The product obtained from the methyl ester of (I; $n = 7$) was found to contain 75% of olefinic acids (by iodine value), and stearic, elaidic, and oleic acids were isolated by fractional crystallisation. A possible mechanism for the formation of olefin is as follows (Barton *et al.*, *loc. cit.*; Seibert, *Ber.*, 1947, **80**, 494) :



Experimental.

Reduction of 9-Keto-10-methoxyoctadecanoic Acid with Sodium and Ethanol.—The acid was obtained, without isolation, from the methyl ester (Part III). Sodium (2 g.) was added to a solution of the acid (1·8 g.) in ethanol (25 c.c.); the mixture was boiled to complete dissolution of the metal and poured into dilute sulphuric acid (200 c.c.; 1N.). The oily product, which slowly crystallised, was eventually separated by filtration and dissolved in boiling methanol (activated charcoal), and the filtered solution evaporated to dryness. Crystallisation of the residue from light petroleum (b. p.

* Part V, preceding paper. † Geneva notation ($CO_2H = 1$) is used for long-chain acids throughout.

60—80°) furnished needles of 9-hydroxyoctadecanoic acid, m. p. 75·5° (yield of material melting at 74°; 0·4 g.) (Found: C, 71·8; H, 11·7. Calc. for $C_{18}H_{36}O_3$: C, 71·9; H, 12·1%). The methyl ester crystallised from aqueous methanol in needles, m. p. 49—50° (Found: C, 72·6; H, 12·0. Calc. for $C_{19}H_{38}O_3$: C, 72·6; H, 12·2%). Tomecko and Adams (*loc. cit.*) gave m. p.s 74—75° and 45—46°, respectively. Oxidation of the hydroxy-acid by chromic acid in acetic acid yielded 9-keto-octadecanoic acid, which separated from ethanol in colourless plates, m. p. 82°. Tomecko and Adams (*loc. cit.*) reported m. p. 82—83°.

Reduction of Methyl 9-keto-10-methoxyoctadecanoate.—(i) *With zinc.* The ester (0·6 g.) in acetic acid (10 c.c.; 70%) was boiled for 10 minutes with zinc dust (4 g.) and concentrated hydrochloric acid (0·1 c.c.). After decantation of the liquid, the zinc was extracted with boiling glacial acetic acid (2 × 10 c.c.) and the combined solutions were poured into water. The crystalline product was filtered off, boiled with excess of sodium hydroxide solution to hydrolyse some ester, and acidified. Crystallisation from aqueous ethanol yielded the product, probably 10-hydroxyoctadecanoic acid, m. p. 79—80° (0·4 g.), which recrystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 81—82°.

Oxidation of this hydroxy-acid with chromic acid in acetic acid furnished 10-keto-octadecanoic acid, which crystallised from ethanol in plates, m. p. 82°. Robinson and Robinson (*loc. cit.*) gave m. p. 83°.

(ii) *By modified Wolff–Kishner method.* A mixture of the ester (2 g.), hydrazine hydrate (3·5 c.c.; 60%), sodium hydroxide (1 g.) in water (1·5 c.c.), and 2 : 2′-dihydroxydiethyl ether (25 c.c.) was boiled under reflux for 1½ hours. Water was then removed by distillation, and the mixture was heated at 200° (internal temp.) for 4 hours (Huang-Minlon, *loc. cit.*) and poured into excess of dilute sulphuric acid, the products being isolated with benzene. Distillation furnished a colourless oil, b. p. 180—190°/0·2 mm. (1·2 g.), which rapidly solidified and contained approx. 75% of octadecenoic acids (Found: Iodine val., 67. Calc. for $C_{18}H_{34}O_2$: Iodine val., 90).

Fractional crystallisation of the product from light petroleum (b. p. 40—60°) at low temperatures yielded stearic acid, m. p. 68—69°, and elaidic acid, m. p. 43—44°; the m. p. of each acid was undepressed by admixture with an authentic specimen. From the mother-liquors, oleic acid was isolated as the lithium salt, which was converted directly into the *p*-phenylphenacyl ester, m. p. and mixed m. p. 60—61°.

In another experiment ethylene glycol was used as solvent during the reduction; the distilled product contained approximately 78% of octadecenoic acids (Found: Iodine val., 70).

We are indebted to the Medical Research Council for a grant which enabled one of us (D. E. A.) to take part in this work.

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613. *Experiments on the Synthesis of Carbonyl Compounds. Part IV.**

By R. E. BOWMAN and W. D. FORDHAM.

The use of acid anhydrides in the synthesis of ketones by the debenzylation process (Bowman, *J.*, 1950, 325) leads to moderate yields of ketones and keto-acids. Whilst other types of carbonyl compounds including amino-ketones, keto-nitriles, and keto-aldehydes have been prepared in the usual manner from the requisite acid chloride with varying degrees of success, all attempts to employ arylmalonic esters proved abortive.

IN Part II (*J.*, 1950, 325) a new and apparently general method of synthesis of saturated ketones was described comprising the following steps:

$$\underset{\text{(I.)}}{R\cdot CH(CO_2Et)_2} \xrightarrow[CH_2Ph\cdot OH]{Na-} R\cdot CNa(CO_2\cdot CH_2Ph)_2 \xrightarrow{R'\cdot COCl} R'\cdot CO\cdot CR(CO_2\cdot CH_2Ph)_2$$

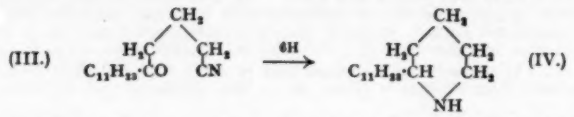
$$\xrightarrow{H^+} R'\cdot CO\cdot CR(CO_2H)_2 \xrightarrow{-2CO_2} \underset{\text{(II.)}}{R'\cdot CO\cdot CH_2R}$$

This paper reports the use of reagents other than acid chlorides, and the preparation of other types of carbonyl compounds. Use of hexanoic, succinic, β-methylglutaric, and glutaric anhydrides in place of the chlorides, and two simple alkylmalonic esters (I; R = *n*-C_6H_{13} and *n*-$C_{12}H_{25}$), gave the desired products but the yields were much inferior, except with glutaric anhydride. Undoubtedly one of the main reasons for the lower yields was the difficulty of decomposing the viscous condensation products which separated from the reaction medium.

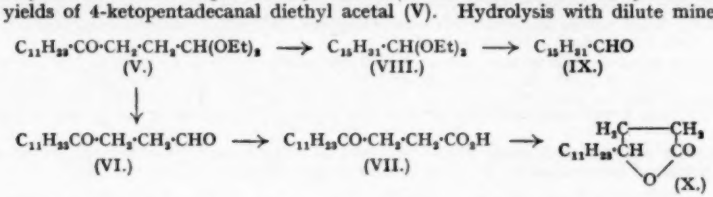
* Part III, *J.*, 1950, 329.

The use of phthalimido-acid chlorides for the preparation of α-amino-ketones was even less successful, only poor yields of the hydrobromides of 2-aminodecan-3-one (II; R′ = $CHMe{\cdot}NH_2$, R = C_6H_{13}) and 1-aminononan-2-one (II; R′ = $CH_2{\cdot}NH_2$, R = C_6H_{13}) being obtained.

In a further variation, the readily accessible ethyl 2-cyanoethylmalonate (R = $CH_2{\cdot}CH_2{\cdot}CN$) (U.S.P. 2,461,336) and decanoyl chloride afforded 1-cyanopentadecan-4-one (III) which on reductive cyclisation over Raney nickel W7 at atmospheric pressure furnished 2-undecylpiperidine (IV), both in excellent yield (cf. Henecka, *Ber.*, 1949, **82**, 104).

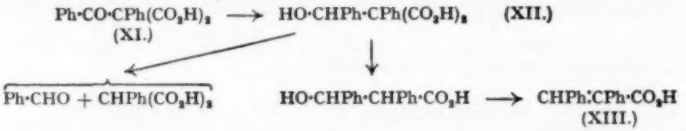


With the exception of the β-compounds, aliphatic keto-aldehydes are almost unknown, and their preparation by our method was therefore studied, using the readily accessible ethyl 2 : 2-diethoxyethylmalonate. After preliminary difficulties this ester and decanoyl chloride gave (60%) yields of 4-ketopentadecanal diethyl acetal (V). Hydrolysis with dilute mineral acid

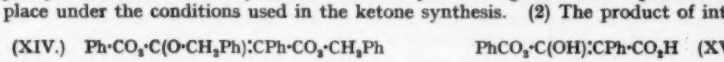


then furnished the free aldehyde (VI). Oxidation of this by alkaline potassium permanganate yielded the keto-acid (VII), and Wolff–Kishner reduction (Huang-Minlon modification, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) of (V) furnished the hexadecanal acetal (VIII) which was hydrolysed to *n*-hexadecanal (IX) (isolated as its oxime). These structures were confirmed by synthesis of the keto-acid (VII) from decanoyl chloride and ethyl ethane-1 : 1 : 2-tricarboxylate. Reduction of (vii) by the Ponndorf method gave the γ-lactone (X).

Attention was next directed to the use of arylmalonic esters and, although we have already described the successful use of an aromatic acid chloride and an alkylmalonate (*loc. cit.*), the results in this case were disappointing. Thus, although *m*-anisoyl chloride and dibenzyl sodiophenylmalonate appeared to react normally to give an aroylmalonate, hydrogenolysis of the latter did not stop abruptly at the amount of hydrogen necessary for debenzylation but proceeded slowly further giving a product from which, after decarboxylation, a small yield of *m*-anisyl phenylketone was obtained. Further, benzoyl chloride and the benzyl ester gave no deoxybenzoin although a small quantity of α-phenylcinnamic acid (XIII) was isolated; in this case hydrogenation proceeded until 2·5 mols. of hydrogen had been taken up. Two possible



explanations for the failures come to mind. (1) Reduction of the carbonyl group in the intermediate aroylmalonic acid (XI) might give the unstable hydroxy-acid (XII) which when heated could either lose water to give (XIII) or be hydrolysed to benzaldehyde and phenylmalonic acid. However, in reduction of simpler compounds such as ethyl benzoyl-*iso*propyl- and -phenyl-malonate and benzoylmethanetricarboxylate no significant absorption of hydrogen took place under the conditions used in the ketone synthesis. (2) The product of interaction



of aroyl chlorides and sodioarylmalonates might consist mainly of the *O*-aroyl derivative (XIV) which would undergo debenzylation to the acid (XV) which could suffer further hydrogenolysis

or, later, hydrolysis to its progenitors.* Although we have no proof that either mechanism takes place we consider it likely that both occur to a significant extent.

We report in the Experimental section some comparative work on variations of the reaction conditions, etc. Two experimental points emerged. First, commercial ethyl methyl ketone is an excellent solvent for the hydrogenation. Secondly, the hydrogenolysis and decarboxylation may be carried out in one step, without sacrifice of yield, by passage of hydrogen through a solution of the benzylacyl-esters in boiling ethyl methyl ketone in the presence of palladised strontium carbonate until evolution of carbon dioxide was complete, a technique which is particularly advantageous on a large scale. During these experiments *n*-tetradecan-6-one and hexadecan-8-one were obtained in a pure condition and characterised as the derived hydantoins (Henze, *J. Amer. Chem. Soc.*, 1942, **64**, 522).

Experimental.

General Method (cf. Part II).—A solution of the requisite malonic ester (1 mol.) and benzyl alcohol (1 mol. per carbethoxy-group of the malonic ester) in benzene (AnalaR) was added to "foamed" sodium ethoxide (1 mol.) in a vacuum and, when dissolution was complete, dry air was admitted. The mixture was distilled through a Fenske column until ester interchange was complete. The acid chloride (0·95 mol.) was then added to the cooled solution and after 30 minutes' refluxing the product was worked up as described previously (*loc. cit.*), hydrogenated in dry ethyl acetate in the presence of 10% palladised strontium carbonate (*ca.* 1 g. per 2 l. of hydrogen), and finally decarboxylated in the usual manner.

Reactions with Acid Anhydrides.—(1) *Hexanoic anhydride.* A solution of the anhydride (19 g., 0·1 mol.; b. p. 107—108°/0·5 mm.) in dry benzene (50 ml.) was added slowly with shaking to a solution of dibenzyl sodiododecylmalonate (0·1 mol.) in benzene, whereupon heat was evolved. The mixture was then refluxed for 0·25 hour and the resulting very viscous mass allowed to cool and decomposed by shaking it vigorously with aqueous acetic acid. After debenzylation and decarboxylation in the usual manner, the product was dissolved in light petroleum (b. p. 40—60°), and acidic material removed by neutralisation with aqueous sodium hydroxide solution. Evaporation of the organic extract furnished pure n-*nonadecan-6-one* (9·2 g., 33%) which separated from light petroleum (b. p. 40—60°) at 0° as colourless plates, m. p. 49° (Found: C, 80·7; H, 13·1. $C_{19}H_{38}O$ requires C, 80·9; H, 13·4%). It formed a *semicarbazone*, prisms (from ethanol), m. p. 66° (Found: N, 12·1. $C_{20}H_{41}ON_3$ requires N, 12·4%).

(2) *Succinic anhydride.* A solution of succinic anhydride (10 g., 0·1 mol.) in boiling benzene (100 ml.) was added quickly to a refluxing solution of dibenzyl sodio-*n*-hexylmalonate (0·1 mol.), and the mixture refluxed for a further 0·5 hour. The resulting thick sludge was cooled and decomposed with dilute sulphuric acid. The product of debenzylation and decarboxylation was heated to 200° to complete the decarboxylation of unchanged malonic acid and then distilled, yielding *4-ketoundecanoic acid* as a colourless oil, b. p. 160—164°/1·5 mm. (4 g., 20%) which solidified immediately and then separated from light petroleum (b. p. 40—60°) in clusters of colourless needles, m. p. 80° (Found: C, 65·8; H, 10·1. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%).

(3) *β-Methylglutaric anhydride.* Prepared as in the previous experiment from the anhydride (12·8 g., 0·1 mol.) and dibenzyl sodio-*n*-dodecylmalonate (0·1 mol.), *5-keto-3-methyloctadecanoic acid* was obtained as a colourless oil, b. p. 196—198°/0·2 mm. (10 g., 32%) which readily solidified and formed colourless plates, m. p. 57·5°, from light petroleum (b. p. 40—60°) (Found: C, 73·4; H, 11·6. $C_{18}H_{34}O_3$ requires C, 73·1; H, 11·5%). Its *p-bromophenacyl* ester crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 71° (Found: C, 63·4; H, 8·2. $C_{27}H_{41}O_4Br$ requires C, 63·6; H, 8·1%).

(4) *Glutaric anhydride.* The viscous, semi-fluid mass resulting from the interaction of the anhydride (11 g., 0·088 mol.) and dibenzyl sodio-*n*-hexylmalonate (0·1 mol.) in benzene was cooled and rendered homogeneous by addition of dry acetone. Decomposition of the sodium salt was then accomplished as in the previous experiment but more readily on account of the lower viscosity of the organic phase. Isolation, debenzylation, decarboxylation, and subsequent distillation furnished *5-ketododecanoic acid* as a colourless oil, b. p. 140—145°/0·3 mm. (11·5 g., 60%). The keto-acid separated from ethyl acetate–light petroleum (b. p. 40—60°) as thin rectangular plates, m. p. 70° (Found: C, 67·3; H, 10·3. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·2%). The *p-phenylphenacyl* ester crystallised from moist ethanol (norite) in colourless laminae, m. p. 103—104° (Found: C, 76·5; H, 7·9. $C_{26}H_{32}O_4$ requires C, 76·5; H, 7·9%).

Amino-ketones.—(1) *2-Aminodecan-3-one hydrobromide.* Oxalyl chloride (16 ml.) was added to a suspension of phthaloylalanine (17·5 g., 0·08 mol.) in dry AnalaR benzene (170 ml.), and since no evident reaction occurred the reaction mixture was heated to the b. p. whereupon a smooth evolution of hydrogen chloride took place and after 1 hour all the solid had dissolved. After 2·5 hours' refluxing, the mixture was slowly distilled through a short Fenske column until the vapour temperature reached 79°, whereafter the remaining solvent was removed under reduced pressure. The resulting acid chloride, which was an almost colourless viscous oil, was dissolved in fresh benzene (100 ml.) and added to a solution of dibenzyl sodio-*n*-hexylmalonate (0·1 mol.) in benzene. The product was isolated, debenzylated, and decarboxylated in the usual manner, the resulting oil diluted with water, and the mixture neutralised with alkali to phenolphthalein. The crude phthalimido-ketone which was isolated

* We are grateful for a suggestion by a Referee that *O*-acylation may predominate in such cases on account of the resulting tendency for the enolate to stabilise itself by conjugation with the benzene ring, *e.g.*, $EtO_2C{\cdot}CPh{:}C(OEt){\cdot}O^-$.

by extraction with benzene–ethyl acetate, was a viscous yellow oil. As it did not crystallise it was hydrolysed by boiling hydrobromic acid (50 ml.; 48%) and acetic acid (50 ml.) for 10 hours. Evaporation to *ca.* 30 ml. gave, on cooling, phthalic acid (2·5 g.; m. p. 200°). The filtrate was decolorised with norite and then evaporated to dryness, furnishing the *hydrobromide* as a crystalline mass (5·2 g., 24%) readily soluble in water, insoluble in ether, but fairly soluble in ethyl acetate from which it separated as colourless, prismatic rods, m. p. 78° after softening at 70° (Found: N, 5·3; Br, 31·4. $C_{16}H_{32}ONBr$ requires N, 5·6; Br, 31·7%).

When an aqueous solution of the hydrobromide was mixed with a slight excess of sodium cyanate in water, an oil separated which solidified on being warmed. 5-n-*Heptyl*-4 : 5(? 3 : 4)-*dihydro*-2-*keto*-4-*methylglyoxaline* crystallised from aqueous ethanol in colourless tablets, m. p. 242° (Found: N, 13·9. $C_{11}H_{20}N_2O$ requires N, 14·3%).

(2) 1-*Aminononan*-2-*one hydrobromide*. From phthaloylglycine chloride (12·5 g., 0·09 mol.; m. p. 82—84°) (Sheenan and Frank, *J. Amer. Chem. Soc.*, 1949, **71**, 1859) and dibenzyl sodio-*n*-hexylmalonate (0·1 mol.) as in the previous experiment, crude *phthalimidononan*-2-*one* was obtained as a viscous oil which slowly solidified (11·5 g.). Although insoluble in light petroleum (b. p. 40—60°) it crystallised, albeit with much loss, from a mixture of that solvent and benzene in yellow prisms, m. p. 44—46°. Removal of the colour could only be effected by repeated crystallisation from light petroleum (b. p. 40—60°)–ethyl acetate, eventually furnishing colourless prisms, m. p. 48° (Found: N, 4·8. $C_{17}H_{21}O_3N$ requires N, 4·8%). The mother-liquors from the crystallisations were evaporated to dryness, to give crude material which was hydrolysed as in the previous experiment. 1-*Aminononan*-2-*one hydrobromide* formed colourless leaflets (from ethyl acetate containing a trace of ethanol) which sintered at 90°, gave a clear mass at *ca.* 120°, and completely liquified at 190° with decomposition (Found: N, 5·8. $C_9H_{19}ONBr$ requires N, 5·9%).

1-*Cyanopentadecan*-4-*one*.—*n*-Dodecanoyl chloride (38 g., 0·17 mol.; b. p. 124°/2 mm.) and dibenzyl sodio-2-cyanoethylmalonate (0·2 mol.) yielded, by the general procedure, a crude product which was boiled with benzene (150 ml.)–ethanol (50 ml.) containing toluene-*p*-sulphonic acid (0·2 g.), under a Fenske column fitted with a Dean and Stark separator until esterification was complete. The cooled solution was washed with potassium hydrogen carbonate solution and water. After the drying (Na_2SO_4) and evaporation of the solvent, the residue was distilled, yielding a fore-run (b. p. 70—150°) and then the *keto-nitrile* as a colourless oil, b. p. 150—154°/0·4 mm. (30 g., 78%), which rapidly solidified and had f. p. 30°. It separated from 96% methanol at 0° in colourless glistening plates, m. p. 30·6—30·8° (Found: C, 76·4; H, 11·4. $C_{16}H_{29}ON$ requires C, 76·4; H, 11·6%).

This (2 g.) with boiling sodium hydroxide (3 ml.; 10N)–ethoxyethanol (10 ml.) (1 hour) gave, after dilution with water and acidification, a quantitative yield of 5-*ketohexadecanoic acid* which separated from light petroleum (b. p. 80—100°) containing a few drops of ethyl acetate as colourless plates (1·7 g.), m. p. 84·5—85·5° (Found: C, 71·4; H, 10·9. $C_{16}H_{30}O_3$ requires C, 71·1; H, 11·1%). Its p-*bromophenacyl* ester crystallised from ethanol in clusters of needles, m. p. 89° (Found: C, 61·4; H, 7·4. $C_{24}H_{33}O_4Br$ requires C, 61·7; H, 7·5%).

2-*Undecylpiperidine*.—The foregoing nitrile (7·5 g.) was hydrogenated in ethanol (100 ml.) in the presence of Raney nickel W7 (Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695) (*ca.* 5 g.) at 50°/1 atm. until absorption of hydrogen ceased (3 mols.). After removal of the catalyst, the filtrate was distilled, yielding the *base* as a colourless oil, b. p. 118—119°/0·3 mm., n_D^{20} 1·4615 (6·5 g., 91%) (Found: C, 80·3; H, 13·7. $C_{16}H_{33}N$ requires C, 80·3; H, 13·8%). Its *hydrochloride* was very sparingly soluble in water but separated from aqueous ethanol in colourless needles, m. p. 138° (Found: N, 5·1. $C_{16}H_{34}NCl$ requires N, 5·05%).

Ethyl 2 : 2-*Diethoxyethylmalonate*.—Previous preparations of the diethyl ester (Perkin and Sprankling, *J.*, 1899, **75**, 13) required the use of pressure equipment but this may be avoided by the following modification: Bromacetal (177 g., 0·9 mol.), prepared in high yield (83—91%) by Bedoukian's method (*J. Amer. Chem. Soc.*, 1944, **66**, 651), was added to a solution of ethyl sodiomalonate (1·25 mols.) in ethanol (400 ml.) containing sodium iodide (2 g.), and the resulting mixture refluxed for 6 hours. Ethanol was removed by distillation with stirring until the bath-temperature reached 160° and refluxing was then continued for a further 3 hours. The thoroughly cooled mixture was then added to water (500 ml.) containing acetic acid (70 ml.), and the product isolated with benzene in the usual manner. Distillation through a Vigreux column furnished unchanged starting materials and then the product as a colourless oil, b. p. 124—125°/2 mm. 114 g., 40%).

Preliminary experiments on the conversion of this material into its dibenzyl ester yielded a dark material, probably owing to the presence of free aldehyde. Accordingly, the ester (100 g.) was purified by slow distillation with a mixture of benzene (200 ml.) and ethanol (50 ml.) containing toluene-*p*-sulphonic acid (0·2 g.) through a Fenske column for 4 hours to convert the free aldehyde into acetal. Anhydrous potassium carbonate (2 g.) was added to the cooled solution, with shaking, followed by water (100 ml.). The ester was then isolated and distilled as before.

4-*Ketopentadecan*-1-*al Diethyl Acetal*.—The foregoing purified ester-acetal (27·6 g., 0·1 mol.) was converted into the sodium derivative of the corresponding dibenzyl ester by means of sodium (2·3 g.; 0·1 mol.) and benzyl alcohol (21·6 g., 0·2 mol.) in benzene (200 ml.) in the usual manner. Decanoyl chloride (20 g., 0·09 mol.) was then added, the mixture refluxed for 30 minutes, and the product isolated, debenzylated, and decarboxylated as described above. Early experiments in which the product was freed from acidic contaminants by neutralisation with alkali yielded a mixture of aldehyde and acetal which were difficult to separate by fractional distillation. Accordingly, the crude product was refluxed with benzene (150 ml.) and ethanol (100 ml.) containing dry hydrogen chloride (1 g.), with azeotropic separation of water, for 8 hours and the product isolated as in the previous experiment. Distillation

furnished the original esters (b. p. 60—158°) and then the *keto-acetal* as a colourless oil, b. p. 158—160°/0·3 mm. (16 g., 60%), which solidified and had f. p. 20—21°. It separated from light petroleum (b. p. 40—60°) at −5° in colourless plates, m. p. 23° (Found: C, 72·9; H, 12·2. $C_{19}H_{38}O_3$ requires C, 72·6; H, 12·1%).

Hydrolysis by boiling N-hydrochloric acid for a few minutes yielded *4-ketopentadecanal* as a solid which crystallised from light petroleum (b. p. 40—60°) at −10° in colourless plates, m. p. 46° (Found: C, 74·7; H, 11·4. $C_{15}H_{28}O_2$ requires C, 75·0; H, 11·6%). The latter reduced both Tollens' reagent and Fehling's solution, formed a *disemicarbazone*, prisms (from ethyl acetate), m. p. 160° (Found: N, 23·4. $C_{19}H_{34}N_6O_2$ requires N, 23·7%), and was oxidised by warm aqueous potassium permanganate–potassium hydrogen carbonate to the corresponding keto-acid (m. p. 92°), identical with the acid synthesised below.

The keto-acetal (5 g.), potassium hydroxide (4·5 g.), hydrazine hydrate (10 ml.; 50%), and 2 : 2′-dihydroxydiethyl ether (30 ml.) were refluxed for 1·5 hours, whereafter the temperature of the mixture was raised to 200° by distillation and kept at that temperature for a further 4 hours. The cooled solution was diluted with water, and the product isolated with light petroleum (b. p. 40—60°). Distillation yielded *n-pentadecanal diethyl acetal* as a colourless mobile oil, b. p. 138—140°/0·6 mm., n_D^{20} 1·4384 (4·3 g., 90%) (Found: C, 75·9; H, 13·2. $C_{19}H_{40}O_2$ requires C, 76·0; H, 13·3%). Hydrolysis with dilute acid gave the free aldehyde characterised as its oxime, needles (from ethanol), m. p. 85° (lit., m. p. 86°), and by oxidation as previously to *n*-pentadecanoic acid, plates (from moist ethanol), m. p. 51° (lit., m. p. 51° and 53°).

4-Ketopentadecanoic Acid.—The keto-ester from decanoyl chloride (21·5 g., 0·098 mol.) and tribenzyl sodioethanetricarboxylate (0·1 mol.) was hydrogenated in ethyl acetate (200 ml.) in the presence of 10% palladised strontium carbonate (4 g.) in the usual manner. The catalyst was filtered off and exhaustively extracted with boiling dry benzene (200 ml. in all). The combined organic extracts were then boiled under reflux for 30 minutes, the solvent was removed, and the residue refluxed with acetic acid (50 ml.)–sulphuric acid (20 ml.; 20N.) for 0·5 hour. After removal of acetic acid in steam, the residue was made alkaline by sodium hydroxide, and the resulting clear solution acidified while hot with hydrochloric acid. The keto-acid was removed from the cooled solution by filtration, dried (24 g., 94%; m. p. 86—89°), and crystallised from benzene as prisms, m. p. 92·5° (Found: C, 70·3; H, 10·5%; equiv., 255. Calc. for $C_{15}H_{28}O_3$: C, 70·3; H, 10·9%; equiv., 256) Asano and Kameda (*J. Pharm. Soc. Japan*, 1941, **60**, 80) reported m. p. 91·5—92·5°. It formed an *oxime*, plates [from light petroleum (b. p. 60—80°)], m. p. 67° (Found: N, 5·37. $C_{15}H_{29}O_3N$ requires N, 5·2%), and a *p-bromophenacyl* ester, needles [from light petroleum (b. p. 40—60°)], m. p. 90° (Found: C, 60·9; H, 7·2. $C_{23}H_{33}O_4Br$. requires C, 60·9; H, 7·5%).

4-Hydroxypentadecanoic Lactone.—The foregoing keto-acid (8 g.) and aluminium *iso*propoxide (5 g.) in *iso*propanol (150 ml.) was submitted to slow distillation through a Fenske column fitted with a variable take-off head until no more acetone distilled off (acetone removed, 2·0 g., estimated as oxime; theory, 1·8 g.). The bulk of the solvent was then removed under reduced pressure and the residue decomposed with dilute sulphuric acid. Isolated with benzene and distilled, the *lactone* was an oil, b. p. 155—157°/0·8 mm., n_D^{20} 1·4590 (7 g.; 93%) which slowly solidified and then separated from light petroleum (b. p. 40—60°) in plates, m. p. 25° (Found: C, 74·9; H, 11·6. $C_{15}H_{28}O_2$ requires C, 75·0; H, 11·7%).

Attempts to Employ Ethyl Phenylmalonate.—(1) *By using* m-*anisoyl chloride.* The acid chloride (17 g., 0·098 mol.) was treated with dibenzyl sodiophenylmalonate (0·1 mol.), and the resulting product hydrogenated according to the general procedure. Absorption of hydrogen, although rapid at first, continued slowly (4 ml./min.) after the theoretical volume (0·2 mol.) had been absorbed. The hydrogenation was stopped and the product worked up as usual. The residue, in benzene, was freed from acids by dilute aqueous sodium hydroxide, and was distilled, giving m-*anisyl phenyl ketone*, a pale yellow oil, b. p. 160—162°/1 mm., n_D^{20} 1·6038 (5·5 g., 24%), which solidified and then separated from ethanol at −20° in colourless needles, m. p. 38·5° (Found: C, 79·6; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%). It formed an *oxime*, plates [from acetone–light petroleum (b. p. 40—60°)], m. p. 117—118° (Found: C, 74·3; H, 6·4; N, 5·8. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2; N, 5·8%).

(2) *By using benzoyl chloride.* The reactants were the acid chloride (0·07 mol.) and dibenzyl sodiophenylmalonate (0·07 mol.). Again hydrogenation proceeded further than that required for debenzylation (0·14 mol.) and, when a total of 4·5 l. (*ca.* 0·2 mol.) had been taken up, was proceeding slowly (0·75 ml./min.). The product was then decarboxylated and separated into neutral and acidic material as in the previous experiment. The former distilled mainly at 140—150°/0·5 mm. as a colourless oil containing only 18% of deoxybenzoin (oxime titration) and was not examined further. The acidic material was esterified azeotropically with ethanol, and the resulting ethyl esters were fractionated *in vacuo*, giving fractions (*a*) b. p. 72—100°/3 mm., mainly ethyl phenylacetate (5·5 g.) and (*b*) b. p. 110—170°/3 mm. (mainly 160°), n_D^{20} 1·5720 (3 g.), ethyl α-phenylcinnamate (100% by sap. equiv.), hydrolysed in good yield to α-phenylcinnamic acid, m. p. 170° alone or mixed with authentic material.

Attempted Reduction of Substituted Benzoylmalonic Esters.—(1) Diethyl benzoyl*iso*propylmalonate (Lund, Hansen, and Voigt, *Kgl. Danske Videnskab. Selskab. Maths-fys. Medd.*, 1933, **12**, 93) formed prisms [from light petroleum (b. p. 60—80°)], m. p. 66° (75%).

(2) Triethyl benzoylmethanetricarboxylate was prepared from benzoyl chloride and sodiomethanetricarbethoxylate in ether (Scholl and Egert, *Annalen*, 1913, **397**, 360) as a colourless oil, b. p. 175—177°/1·2 mm., n_D^{20} 1·5042, which just solidified at room temperature.

(3) *Ethyl benzoylphenylmalonate*, prepared from benzoyl chloride (1 mol.) and sodiophenylmalonate (1 mol.) in benzene in the usual manner, was an oil which after removal of material volatile up to

100°/0·5 mm. solidified and then crystallised from benzene–light petroleum (b. p. 60—80°) in elongated prisms, m. p. 79° (Found: C, 70·5; H, 5·9. $C_{20}H_{20}O_3$ requires C, 70·6; H, 5·9%).

Attempts to hydrogenate esters from (1) and (3) by using palladised strontium carbonate in ethyl acetate were unsuccessful; in the case of the second ester, a very slow uptake of hydrogen occurred but the products were not isolated.

Miscellaneous Experiments.—(1) n-*Tetradecan-6-one*. The product from *n*-nonanyl chloride and dibenzyl sodio-*n*-butylmalonate was hydrogenolysed, decarboxylated, and freed from solvent at 120°. The residual oil, in light petroleum (b. p. 40—60°), was washed with dilute sodium hydroxide solution, dried, and distilled. The *ketone*, b. p. 112—114°/1 mm., solidified (f. p. 24—25°) and then separated from methanol in plates, m. p. 25° (Found: C, 79·0; H, 13·1. $C_{14}H_{28}O$ requires C, 79·2; H, 13·2%); the derived *hydantoin* formed prismatic needles (from methanol), m. p. 111° (Found: N, 10·2. $C_{18}H_{30}O_2N_2$ requires N, 9·9%).

The hydrogenation was carried out at the b. p. of the solvent (150 ml.) by passage of a brisk stream of hydrogen in the presence of 10% palladised strontium carbonate (3 g. per 0·1 mol.) for 15 minutes after evolution of carbon dioxide (lime-water) had ceased. The following solvents were used (yields in parentheses): ethyl acetate (65%), ethyl acetate–10% acetic acid (60%), and ethyl methyl ketone (65%).

(2) *Hexadecan-8-one*. The reaction, as before, of *n*-nonanyl chloride and dibenzyl sodio-*n*-hexylmalonate furnished the *ketone*, b. p. 125—127°/1 mm., which solidified and then separated from methanol in lustrous plates, m. p. 37° (Found: C, 80·3; H, 13·2. $C_{16}H_{32}O$ requires C, 80·0; H, 13·3%), and formed a *hydantoin*, colourless needles (from methanol), m. p. 124° (Found: N, 8·8. $C_{18}H_{34}O_2N_2$ requires N, 9·0%).

(*a*) The hydrogenation was effected in boiling ethyl methyl ketone as before. The addition of acid (chloride was carried out (i) at room temperature, with, later, refluxing for 30 minutes (yield, 65%), (ii) at the b. p. (yield, 60%), and (iii) at 0°, with, later, storage at this temperature for 24 hours yield, 70%).

(*b*) Hydrogenation was effected in boiling ethyl methyl ketone containing (i) 5% of water (yield, 57%) and (ii) 5% of acetic anhydride (yield, 67%).

(*c*) The hydrogenation was carried out in ethyl methyl ketone at room temperature in the usual manner (yield, 65%).

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614. *Experiments on the Synthesis of Carbonyl Compounds. Part V.* β-Keto-esters and -nitriles.*

By R. E. BOWMAN and W. D. FORDHAM.

β-Keto-esters and -nitriles may be prepared by hydrogenolysis and subsequent decarboxylation of benzyl ethyl acylmalonates and benzyl acylcyanoacetates respectively.

THE debenzylation process using dibenzyl esters of substituted acylmalonic esters has been used for the synthesis of ketones (Bowman, *J.*, 1950, 325). We now report the use of monobenzyl esters for the synthesis of β-keto-esters and -nitriles.

Benzyl ethyl malonate was readily obtained by alcoholysis of the diethyl ester with benzyl alcohol in the presence of a catalytic amount of sodium ethoxide. Reaction of its sodio-derivative (I; R′ = H, 2 mols.) with an acid chloride and subsequent hydrogenolysis and decarboxylation furnished the β-keto-esters (II; R = C_7H_{15} and $C_{11}H_{23}$, R′ = H) in 70% yield.

$$R\cdot COCl + \underset{(I.)}{CH_2Ph\cdot O_2C\cdot CR'Na\cdot CO_2Et} \longrightarrow R\cdot CO\cdot CR'(CO_2\cdot CH_2Ph)\cdot CO_2Et \xrightarrow[-CO_2]{H_2\text{-}Pd} \underset{(II.)}{R\cdot CO\cdot CHR'\cdot CO_2Et}$$

For α-substituted β-keto-esters the requisite benzyl ethyl alkylmalonates were prepared by interaction of the crude sodium salt of the half acid-ester and benzyl chloride or, more conveniently, by partial alcoholysis. Reaction as before gave the β-keto-esters (II; R = $C_{11}H_{23}$, R′ = CHMeEt·CH_2, and R = C_8H_{17}·CH·OMe, R′ = Me), in the latter case accompanied by the ketone (III) and the ester (IV) formed by trans-esterification.

(III.) $C_8H_{17}\cdot CH(OMe)\cdot CO\cdot C_7H_{15}$ $C_8H_{17}\cdot CH(OMe)\cdot CO\cdot CMe\cdot(CO_2Et)_2$ (IV.)

A trans-esterification equilibrium was realised experimentally in boiling benzene and limits the yield of β-keto-ester.

* Part IV, preceding paper.

For the preparation of β-keto-nitriles, the requisite benzyl sodiocyanoacetate was generated *in situ* (cf. *J.*, 1950, 177, 325), ester-interchange being highly satisfactory although ethyl

$$CN\cdot CHR'\cdot CO_2Et \xrightarrow[CH_2Ph\cdot OH]{Na-} CN\cdot CR'Na\cdot CO_2\cdot CH_2Ph \xrightarrow[H_2\text{-}Pd;\ -CO_2]{R\cdot COCl;} R\cdot CO\cdot CHR'\cdot CN \quad (V.)$$

sodiocyanoacetate and the corresponding benzyl ester were sparingly soluble. Subsequent hydrogenation and decarboxylation furnished (V; R = C_9H_{19} and Ph, R′ = H) in 80% yields. α-Substituted β-keto-nitriles may be prepared in a similar manner, *e.g.*, (V; R = C_9H_{17}, R′ = $CHMe\cdot C_6H_{13}$; R = C_9H_{17} or $C_{11}H_{23}$, R′ = Bu).

It may be noted that the sodio-derivatives of the α-substituted keto-nitriles are more stable in boiling ethanol than are the parent β-keto-esters (cf., *inter al.*, Renfrew, *J. Amer. Chem. Soc.*, 1944, **66**, 144) since the keto-nitrile (V; R = C_9H_{17}, R′ = Bu) and *n*-octyl bromide in the presence of ethanolic sodium ethoxide gave the disubstituted product (VI) in 82% yield. Hydrolysis of the substituted keto-nitrile with aqueous sulphuric acid gives the corresponding ketone, whereas attempts to obtain the derived β-keto-ester from the keto-nitrile (V; R = C_9H_{17}, R′ = Bu) by means of ethanolic hydrogen chloride were unsuccessful, the corresponding amide (VII) being formed (cf. Dorsch and McElvain, *ibid.*, 1932, **54**, 2960).

(VI.) $C_9H_{17}\cdot CO\cdot CBu(C_9H_{17})\cdot CN$ $\qquad$ $C_9H_{17}\cdot CO\cdot CHBu\cdot CO\cdot NH_2$ (VII.)

Experiments on the synthesis of carbonyl compounds without the use of hydrogenation are in progress.

Experimental.

Benzene (AnalaR) and ether were dried by sodium.

Unless otherwise specified, the techniques were as described in Part II (*loc. cit.*), catalytic debenzylation being carried out in ethyl methyl ketone by use of palladised strontium carbonate either at room temperature with subsequent decarboxylation (method A; Part II) or at the b. p. with simultaneous decarboxylation of the keto-acids (method B; see Part IV, preceding paper).

Benzyl Ethyl Malonate.—A mixture of ethyl malonate (320 g., 2 mols.), benzyl alcohol (108 g., 1 mol.), and benzene (200 ml.) was distilled slowly through a Fenske column fitted with a variable reflux-head until any water present was removed and, after slight cooling, sodium ethoxide in ethanol (20 ml. of 10%) was added. Benzene–ethanol azeotrope (b. p. 68—69°) was then distilled off until interchange was complete, and the cooled mixture was washed with dilute sulphuric acid, then water, and dried (Na_2SO_4). Fractionation through a short Fenske column *in vacuo* yielded ethyl malonate (b. p. 55—60°/1·5 mm.; 120 g.), an intermediate fraction (b. p. 60—123°/1·5 mm., 40 g.), and benzyl ethyl malonate, a colourless oil, b. p. 123—125°/1·5 mm. (mainly 124/1·5 mm.) (165 g., 74%). A residue of *ca.* 30 g. was presumably the dibenzyl ester; the use of less malonic ester gave more of the dibenzyl ester but caused no difficulty in isolation of the product.

Acylacetic Esters, $R\cdot CO\cdot CH_2\cdot CO_2Et$.—Benzyl ethyl malonate (0·2 mol.) was added in ether (100 ml.) to powdered sodium (0·2 mol.) under ether (200 ml.) in the usual manner and, when dissolution of the metal was complete, the acid chloride (0·1 mol.) was added dropwise with stirring. After 0·5 hour's refluxing the cooled suspension of sodio-derivative was filtered off and the residue washed with dry ether and then decomposed by shaking a suspension of it in ether with dilute sulphuric acid. The dried organic extract was evaporated and the residue hydrogenated and decarboxylated (method A). Distillation then yielded the keto-ester in 60—70% yield. In this manner, octanoyl and dodecanoyl chloride furnished ethyl 3-ketodecanoate, b. p. 82—84°/0·3 mm., and 3-ketotetradecanoate, b. p. 128—130°/0·3 mm., respectively, identical with specimens prepared previously (Part I; *J.*, 1950, 322).

Benzyl Ethyl iso*Amylmalonate.*—Potassium hydroxide (13 g.) and ethyl *iso*amylmalonate (46 g., 0·2 mol.) in ethanol (200 ml.) were left overnight and the product was then evaporated to dryness under reduced pressure. Benzyl chloride (26 g., 0·2 mol.) was added, together with sodium iodide (2 g.) and pyridine (1 ml.), the mixture was heated under reflux at 160° for 6 hours, cooled, and poured into water, and the resulting oil extracted with benzene. After being washed with sodium hydrogen carbonate solution, then water and dried, the organic extract was distilled, giving the *ester* as a colourless oil, b. p. 126—128°/0·1 mm., n_D^{20} 1·4822 (30 g., 52%) (Found: C, 70·1; H, 8·6. $C_{17}H_{24}O_4$ requires C, 69·9; H, 8·3%).

Ethyl 2-iso*Amyl*-3-*ketotetradecanoate.*—The foregoing ester (22 g., 0·075 mol.) in dry ether (100 ml.) was converted into its sodio-derivative with sodium (1·73 g.; 0·075 mol.) under ether as above, and decanoyl chloride (16·4 g., 0·074 mol.) added. After 0·5 hour's refluxing the cooled reaction mixture was washed with aqueous acid and then evaporated *in vacuo*. The product obtained after hydrogenation and decarboxylation (method A) was dissolved in light petroleum (b. p. 40—60°; 150 ml.) and washed with water and dilute aqueous potassium hydrogen carbonate. Distillation gave, after a forerun, the *keto-ester* as a colourless oil, b. p. 151—152°/0·2 mm., n_D^{20} 1·4471 (15·5 g., 60%) (Found: C, 73·7; H, 11·7. $C_{21}H_{40}O_3$ requires C, 74·1; H, 11·8%).

Benzyl Ethyl Methylmalonate.—Prepared from methylmalonic ester (155 g.; *Org. Synth.*, 1937, **17**, 56) and benzyl alcohol (48 g.) as was the unmethylated analogue, the *ester* had b. p. 134—136°/1 mm., n_D^{20} 1·4892 (75 g., 70%) (Found: C, 66·3; H, 7·0%; sap. equiv., 119. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%; sap. equiv., 118).

Ethyl 3-Keto-4-methoxy-2-methyldodecanoate.—By interaction of 2-methoxydecanoyl chloride (37 g., 0·16 mol.) and benzyl ethyl sodiomethylmalonate (0·2 mol.) as in the previous experiment and subsequent hydrogenation and decarboxylation (method A), an oil (50 g.) of b. p. 85—155°/0·3 mm. was obtained. Fractionation yielded fractions, (*A*) b. p. 50—84°/0·3 mm., (*B*) b. p. 120—130°/0·3 mm., and (*C*) b. p. 134—142°/0·3 mm.

Fraction (*A*) was a mixture of ester (22% as diethyl methylmalonate) and ketone. The former was removed by an excess of boiling ethanolic potassium hydroxide; after removal of ethanol in steam, the ketone was isolated in the usual manner. *3-Keto-4-methoxydodecane* thus obtained, b. p. 81—82°/0·4 mm., n_D^{20} 1·4361 (Found: C, 72·5; H, 11·9. $C_{13}H_{26}O_2$ requires C, 72·9; H, 12·1%), formed a *semicarbazone*, short prisms (from aqueous methanol), m. p. 118° (Found: N, 15·3. $C_{14}H_{29}O_2N_3$ requires N, 15·5%).

Fraction (*B*) on refractionation yielded the *keto-ester*, b. p. 122—124°/0·2 mm., n_D^{20} 1·4430 (12 g., 26%) (Found: C, 66·7; H, 10·6. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·5%), which gave a deep red colour with aqueous-ethanolic ferric chloride. The derived *pyrazolone* formed colourless plates, m. p. 75° (Found: N, 8·55. $C_{20}H_{36}O_2N_2$ requires N, 8·48%).

Fraction (*C*) on redistillation gave *diethyl 3-keto-4-methoxydodecane-1 : 1-dicarboxylate*, b. p. 142—144°/0·3 mm., n_D^{20} 1·4478 (Found: C, 63·7; H, 9·8. $C_{19}H_{34}O_6$ requires C, 63·7; H, 9·5%).

Acylacetonitriles, R·CO·CH_2·CN.—A mixture of benzyl alcohol (0·25 mol.) and ethyl cyanoacetate (0·25 mol.) was added in benzene (200 ml.) to "foamed" sodium ethoxide (0·25 mol.; *J.*, 1950, 325) under benzene (400 ml.) and the resulting suspension distilled (oil-bath) through a Fenske column until ester interchange was complete (see Part II). The acid chloride (0·125 mol.) was then added and the mixture refluxed for 0·5 hour. If the resulting sodio-derivative was insoluble it was filtered off and treated as in the case of the unsubstituted β-keto-ester; if the sodio-derivative was soluble, the cooled mixture was shaken with ice-cold dilute sulphuric acid and after removal of solvent was hydrogenated and distilled as before.

From *n*-decanoyl chloride, by method (B), *1-cyanoundecan-2-one* was obtained; it had b. p. 111—113°/0·3 mm. and solidified readily and then separated from methanol in plates, m. p. 58—58·5° (80%) (Found: C, 73·5; H, 11·0. $C_{12}H_{21}ON$ requires C, 73·8; H, 10·8%). It gave a deep red ferric reaction and formed a 2 : 4-*dinitrophenylhydrazone* which separated from ethanol in orange-yellow needles, m. p. 66° (Found: C, 57·6; H, 6·4. $C_{18}H_{25}O_4N_5$ requires C, 57·6; H, 6·7%).

Phenylacetyl chloride gave similarly (method B; 80%) *1-cyano-3-phenylacetone*, b. p. 116°/0·5 mm., n_D^{20} 1·5370, which gave a deep red colour with aqueous-ethanolic ferric chloride (Found: C, 75·4; H, 6·0. $C_{10}H_9ON$ requires C, 75·5; H, 5·7%) and a 2 : 4-*dinitrophenylhydrazone*, yellow needles (from ethanol), m. p. 130° (Found: C, 56·1; H, 3·5. $C_{16}H_{13}O_4N_5$ requires C, 56·5; H, 3·8%).

α-*Substituted β-Ketonitriles*, R·CO·CHR′·CN.—The procedure was that used in the previous experiments, except that the reactants were benzyl alcohol (1 mol.), ethyl alkylcyanoacetate (1 mol.), sodium (1 mol.), and the acid chloride (0·95 mol.); none of the products gave a ferric reaction.

5-Cyanotetradecan-4-one. Pelargonyl chloride and benzyl sodio-*n*-butylmalonate gave the *keto-nitrile*, b. p. 122—123°/0·5 mm., n_D^{20} 1·4526 (method A; 63%) (Found: C, 75·7; H, 11·1. $C_{15}H_{27}ON$ requires C, 75·9; H, 11·4%). It formed an *oxime*, glistening colourless needles [from light petroleum (b. p. 80—100°)], m. p. 54—54·5° (Found: N, 10·6. $C_{15}H_{28}ON_2$ requires N, 11·1%), and was hydrolysed by refluxing it (5 g.) with sulphuric acid (20N.) and propionic acid (15 ml.) for 10 hours to give tetradecan-6-one, m. p. 24° (3·5 g.) undepressed on admixture with an authentic specimen (see Part IV, *loc. cit.*).

9-Butyl-9-cyano-octadecan-10-one. The foregoing nitrile (5 g.) was added to a solution of sodium ethoxide (from 0·5 g. of metal) in ethanol (20 ml.), and *n*-octyl bromide (8 g.) was added. The mixture was refluxed for 4 hours whereafter most of the ethanol was removed by distillation and the cooled residue treated with cold dilute sulphuric acid. The product was isolated with benzene and distilled, giving the *ketone*, b. p. 174—176°/0·5 mm., n_D^{20} 1·4590 (6 g., 82%) (Found: C, 78·8; H, 12·1. $C_{28}H_{55}ON$ requires C, 78·9; H, 12·3%).

2-Butyl-3-ketoundecanoamide. A solution of 5-cyanotetradecan-4-one (5 g.) in absolute ethanol (4 ml.) was saturated with dry hydrogen chloride and set aside at room temperature for 7 days. The mixture was then poured into water, giving the *keto-amide* which was filtered off. It separated from boiling benzene in prisms, m. p. 113° (Found: C, 70·3; H, 11·1; N, 5·7. $C_{15}H_{29}O_2N$ requires C, 70·6; H, 11·4; N, 5·5%).

5-Cyanoheptadecan-6-one. From benzyl sodio-*n*-butylcyanoacetate and decanoyl chloride, the *keto-nitrile* was obtained having b. p. 146—147°/0·1 mm.; it rapidly solidified and had f. p. 34° (Found: C, 77·1; H, 11·4. $C_{18}H_{33}ON$ requires C, 77·2; H, 11·7%).

8-Cyano-7-methylheptadecan-9-one. This *keto-nitrile* was prepared from nonanoyl chloride and benzyl sodio-1′-methylheptylcyanoacetate (method A; 80%); it had b. p. 154—156°/0·5 mm., n_D^{20} 1·4550 (Found: C, 77·9; H, 11·9; N, 4·5. $C_{19}H_{35}ON$ requires C, 77·8; H, 11·9; N, 4·8%). The product was recovered unchanged after being treated with boiling ethanolic sodium ethoxide (1 mol.) for 8 hours.

One of us (W. D. F.) thanks the directors of Messrs. A. Boake, Roberts and Co. Ltd. for facilities for carrying out part of the work described in this and the previous paper.

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615. *Quaternary Ammonium Salts. Part II.* The Formation and Decomposition of Diethylmethylanilinium Salts. Route to N-Ethyl-N-methylanilines.*

By Hussein A. Fahim and Abdallah M. Fleifel.

Diethylanilines, now obtained in good yields from the primary bases by treatment with ethyl sulphate, give the quaternary diethylmethylanilinium salts more readily with methyl iodide than with methyl sulphate. The quaternary salts from diethyl-*m*- and -*o*-toluidine and methyl iodide can be obtained at the room temperature, but *o*-chloro-*NN*-diethyl-, *NN*-diethyl-*o*-, *m*-, and -*p*-nitro-, and *NN*-diethyl-4-methyl-2-nitro-aniline do not give the quaternary salt under any conditions tried with either reagent. Thermal or alkaline decomposition of the quaterary salts studied takes place smoothly in one direction, to give invariably the *N*-ethyl-*N*-methyl-anilines, except that *NN*-diethyl-*N*-methyl-*p*-phenetidinium iodide gives diethyl-*p*-phenetidine.

Experimental.—The general procedures were those described in Part I.*

NN-Diethyl-*p*-anisidine was obtained (61% yield) when *p*-anisidine (50 g., 1 mol.) and ethyl sulphate (130 g., 2·2 mols.) were heated at 120—130° for 4 hours. *NN*-Diethyl-*N*-methyl-*p*-anisidinium iodide was obtained in quantitative yield when equimolecular amounts of diethyl-*p*-anisidine and methyl iodide reacted overnight at the room temperature; the corresponding *picrate*, obtained in 69·5% yield when equimolecular amounts of the tertiary base and methyl sulphate were heated at 120—130° for 4 hours and the neutralised reaction mixture was treated with saturated picric acid solution, crystallised from water and melted at 108° (Found: C, 51·5; H, 5·2; N, 13·3. $C_{18}H_{23}O_8N_4$ requires C, 51·2; H, 5·2; N, 13·3%).

Diethyl-*o*-anisidine, obtained in 42·5% yield when *o*-anisidine (80 g., 1 mol.) and ethyl sulphate (188 g., 2·2 mols.) were heated at 120—130° for 6 hours, had b. p. 226°. Its *picrate* crystallised from water and melted at 135—136° (Found: C, 49·7; H, 4·9; N, 13·6. $C_{17}H_{20}O_8N_4$ requires C, 50·0; H, 4·9; N, 13·7%). *NN-Diethyl-N-methyl-o-anisidinium iodide*, obtained in 75·3% yield from the tertiary base and methyl iodide (1 mol. each) at 80° (4 hours), crystallised from methanol–ether and melted at 219—220° (Found: I, 39·9. $C_{12}H_{20}ONI$ requires I, 39·6%). The *picrate*, obtained in 60·8% yield by use of methyl sulphate at 120—130° (7 hours), had m. p. 120—121° (from water) (Found: C, 50·6; H, 5·2; N, 13·4. $C_{18}H_{22}O_8N_4$ requires C, 51·2; H, 5·2; N, 13·3%). The *perchlorate* crystallised from water and melted at 114—115° (Found: Cl, 11·9. $C_{12}H_{20}O_5NCl$ requires Cl, 12·0%).

Unless otherwise stated, the following were similarly prepared.

Diethyl-*p*-phenetidine (58% yield; 7 hours; b. p. 260°) gave the *picrate* (from ethanol), m. p. 110—111° (Found: C, 51·0; H, 5·0; N, 13·4. $C_{18}H_{22}O_8N_4$ requires C, 51·2; H, 5·2; N, 13·3%). *NN-Diethyl-N-methylphenetidinium iodide*, obtained in 74·1% yield from the tertiary base and methyl iodide (1 mol. each) at room temperature (2 days), crystallised from methanol–ether and melted at 142—143° (Found: I, 38·6. $C_{13}H_{22}ONI$ requires I, 37·9%). The *picrate*, obtained in 66·7% yield by use of methyl sulphate at 120—130° (4 hours), crystallised from water and melted at 91·5—92·5° (Found: C, 52·2; H, 5·7; N, 13·0. $C_{19}H_{24}O_8N_4$ requires C, 52·3; H, 5·5; N, 12·8%).

NN-Diethyl-*m*-phenetidine (52% yield; 8 hours) gave a *picrate*, m. p. 130—131° (from ethanol) (Found: C, 51·2; H, 5·3; N, 13·2%). *N-Ethyl-N-methyl-m-phenetidine picrate* crystallised from ethanol and melted at 127° (Found: C, 50·0; H, 5·0; N, 13·5. $C_{17}H_{20}O_8N_4$ requires C, 50·0; H, 4·9; N, 13·7%). *NN-Diethyl-N-methylphenetidinium iodide*, obtained in 64·7% yield by keeping the tertiary base and methyl iodide (1 mol. each) at room temperature for 3 days, crystallised from acetone–ether and melted at 137—138° (Found: I, 37·6%). The corresponding *picrate*, obtained in 51·5% yield by use of methyl sulphate (1 mol.) at 120—130° (4 hours), had m. p. 101—102° (from aqueous acetone) (Found: C, 52·3; H, 5·4; N, 12·9%).

NN-Diethyl-*o*-phenetidine (54·6% yield; 7 hours) gave the *picrate*, m. p. 111° (from ethanol) (Found: C, 51·0; H, 5·2; N, 13·3%). *NN-Diethyl-N-methyl-o-phenetidinium iodide*, obtained in 61·2% yield by use of methyl iodide (1 mol.) at 80° (4 hours), crystallised from methanol–ether and melted at 194—195° (Found: I, 37·4%). The *picrate*, obtained in 45·5% yield by use of methyl sulphate (1·5 mols.) at 120—130° (10 hours), had m. p. 119° (from water) (Found: C, 52·2; H, 5·6; N, 12·7%). The *perchlorate*, crystallised from water, had m. p. 115—116° (Found: Cl, 11·7. $C_{13}H_{22}O_5NCl$ requires Cl, 11·5%).

NN-Diethyl-*p*-toluidine, obtained in 91·3% yield at 120—130° (6 hours), gave a *picrate*, 110° (from ethanol) (Found: C, 52·0; H, 5·2; N, 14·5. $C_{17}H_{22}O_7N_4$ requires C, 52·0; H, 5·1; N, 14·3%). *Diethylmethyl-p-toluidinium iodide*, obtained in 59·4% yield by use of methyl iodide at room temperature (overnight) and crystallised from ethanol–ether, had m. p. 165° (Found: I, 41·8. $C_{12}H_{20}NI$ requires I, 41·6%). The *picrate*, obtained in 53% yield from the tertiary base (1 mol.) and methyl sulphate (2 mols.) at 120—130° (2 hours), crystallised from water and melted at 105—106° (Found: C, 52·9; H, 5·3; N, 13·8. $C_{18}H_{22}O_7N_4$ requires C, 53·2; H, 5·4; N, 13·8%).

* The following paper is to be regarded as Part I: *J.*, 1950, 3529.

NN-Diethyl-*m*-toluidine (84% yield; 6 hours) gave the *picrate*, m. p. 124° (from ethanol) (Found: C, 52·2; H, 5·0; N, 14·3%). *Diethylmethyl*-m-*toluidinium iodide*, obtained in 57·7% yield from the tertiary base and methyl iodide (1 mol. each) at room temperature (2 weeks) (no quaternary salt could be isolated when the temperature was raised), crystallised from acetone–ether and melted at 109—110° (Found: I, 41·2%). The *picrate*, obtained in 48% yield by use of methyl sulphate (2 mols.) at 120—130° (24 hours), had m. p. 136—137° (from water) (Found: C, 53·4; H, 5·4; N, 13·9%).

NN-Diethyl-*o*-toluidine (35% yield; 6 hours) gave the *picrate*, m. p. 181—182° (from ethanol) (Found: C, 52·3; H, 5·0; N, 14·2%). *Diethylmethyl*-*o*-*toluidinium iodide*, obtained in 14·4% yield from the tertiary base and methyl iodide at room temperature (2 months) (no quaternary salt could be isolated when the temperature was raised), crystallised from methanol–ether and melted at 137—138° (Found: I, 41·8%). The *picrate*, obtained in 8% yield from the tertiary base and methyl sulphate (6 mols.) at 120—130° (32 hours), had m. p. 129° (from water) (Found: C, 53·1; H, 5·3; N, 13·9%).

p-*Bromo*-NN-*diethylanilinium picrate* crystallised from ethanol and melted at 163° (Found: C, 42·6; H, 4·0; N, 12·4; Br, 17·7. $C_{18}H_{17}O_7N_4Br$ requires C, 42·0; H, 3·7; N, 12·3; Br, 17·5%). p-*Bromo*-NN-*diethyl*-*N*-*methylanilinium iodide*, obtained in 75% yield by use of methyl iodide (1 mol.) at about 100° (1 hour) and crystallised from methanol–ether, melted at 189—190° (Found: total halogen, 56·2. $C_{11}H_{17}NBrI$ requires total halogen, 55·9%). The *picrate*, obtained from the iodide and crystallised from ethanol, melted at 165—166° (Found: C, 43·7; H, 3·9; N, 12·0; Br, 17·2. $C_{17}H_{16}O_7N_4Br$ requires C, 43·3; H, 4·0; N, 11·9; Br, 17·0%). The *perchlorate* crystallised from water and melted at 180—181° (Found: total halogen, 34·0. $C_{11}H_{17}O_4NBrCl$ requires total halogen, 33·7%).

m-Bromo-*NN*-diethylaniline (59·3% yield; 7 hours) gave the *picrate* which crystallised from ethanol and melted at 118° (Found: C, 42·3; H, 3·9; N, 12·0; Br, 17·8%). m-*Bromo*-NN-*diethyl*-*N*-*methylanilinium iodide*, obtained in 37·5% yield by use of methyl iodide (1 mol.) at about 100° (8 hours) and crystallised from methanol–ether, had m. p. 184—185° (Found: total halogen, 56·3%). The *picrate*, obtained from the iodide, crystallised from ethanol and melted at 125—126° (Found: C, 42·7; H, 3·8; N, 12·0; Br, 17·1%). The *perchlorate* had m. p. 105—106° (from water) (Found: total halogen, 33·5%).

o-Chloro- (47·5% yield; 8 hours) and *o*-nitro-*NN*-diethylaniline (53% yield; 8 hours) and *NN*-diethyl-2-nitro-4-methylaniline (65·8% yield; 10 hours) were also prepared.

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616. *The Fluorination of Some Nitrides and Cyanides.*

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PARTLY with a view to the preparation of nitrogen trifluoride, some experiments have been carried out on the fluorination of a few nitrides and cyanides.

Magnesium nitride did not react even with undiluted fluorine, either at room temperature or when the copper reaction tube was heated to about 400°. Boron nitride, on the other hand, reacted vigorously, as reported by Moissan and Lebeau (*Compt. rend.*, 1900, **130**, 1436) who did not, however, determine the fate of the nitrogen: fractionation of the gaseous reaction product gave only boron trifluoride.

Reactions between cyanides and fluorine have been reported by Moissan (*Ann. Chim. physique*, 1891, **24**, 262) who did not investigate the reaction products, and by Ruff and Geise (*Ber.*, 1936, **69**, 598), who obtained a variety of products from silver cyanide, including carbon tetrafluoride, perfluoromethylamine ($CF_3 \cdot NF_2$) inseparably mixed with perfluoroethane, and compounds of composition $C_2N_2F_6$ and $C_2N_2F_8$. The reaction between gaseous fluorine and solid potassium ferro- and ferri-cyanide, and between gaseous hydrogen cyanide and solid cobalt trifluoride have now been studied. The ferro- and ferri-cyanides were chosen since they can readily be obtained pure and dry. Both react readily with fluorine diluted with nitrogen, and give a large number of gaseous products, some of which rapidly attack both mercury and tap grease and make manipulation rather difficult. Only two definite compounds have been isolated from these mixtures, *viz.*, carbon tetrafluoride and perfluoromethylamine; no hexafluoroethane was found, so that the perfluoromethylamine could be isolated. This compound has also been obtained by Haszeldine (*J.*, 1950, 1966) as a by-product in the fluorination of methylaniline, and by fluorination of methylamine, both by cobalt trifluoride. Since the boiling points of perfluoroethane and perfluoromethylamine are −78·2° and −77·0°, respectively, separation by fractional distillation is impracticable. The vapour pressure of perfluoromethylamine, measured from −135° to −75° and, above its m. p. of −122·1° follows the equation, $\log_{10} p_{mm.} = 7{\cdot}474 - 901{\cdot}0/T$, which gives the latent heat of vaporisation as 4·12 kcals./mole, and the Trouton constant as 21·0. The vapour pressure below the m. p.

(*i.e.*, of the solid) is given, less accurately, by $\log_{10} p_{mm.} = 7{\cdot}95 - 970/T$. The triple-point pressure was $32{\cdot}_2$ mm.

The fluorination of anhydrous hydrogen cyanide, by cobalt trifluoride at 200—250°, with nitrogen as diluent, also gave a variety of products. No single substance except carbon tetrafluoride could be isolated by fractional distillation. No perfluoromethylamine could be isolated since it was mixed with hexafluoroethane. A fraction b. p. −38·0° to −39·1°, of molecular weight 161—171, evidently consisted mainly of $C_3N_3F_9$ (*M*, 166; Ruff and Geise, *loc. cit.*) together with some $C_3N_3F_8$ (*M*, 204). A very complex mixture of compounds of higher molecular weight containing carbon, nitrogen, and fluorine was also obtained; it was unreactive to all reagents tested except hot potassium.

Since the fluorination of hydrocarbons substituted by CF_3 groups gives higher yields of fluorocarbons and fewer by-products than the fluorination of unsubstituted hydrocarbons, it was expected that treatment of trifluoromethyl cyanide with cobalt trifluoride would give a substantial yield of perfluoroethylamine, $C_2F_5{\cdot}NF_2$. In fact, the major product was hexafluoroethane, but perfluoroethylamine, b. p. −34·3°, was also obtained. This substance is unreactive and non-basic, like perfluoromethylamine; its vapour pressure, measured from −102° to −37°, is given by: $\log_{10} p_{mm.} = 7{\cdot}435 - 1088/T$, which gives the latent heat of vaporisation as 4·98 kcals./mole, and the Trouton constant as 20·8. The liquid forms a glass when cooled in liquid oxygen. It is interesting that the boiling point is somewhat higher than the value −37·0° found by Thompson and Emeléus (*J.*, 1949, 3080) for the isomeric secondary compound perfluorodimethylamine $(CF_3)_2NF$, prepared by the cobalt fluoride fluorination of trimethylamine.

Experimental.—Fluorinations with gaseous fluorine were carried out in apparatus constructed from copper tube, and those with cobalt trifluoride in a horizontal tubular reactor containing 20 lb. of cobalt trifluoride which could be stirred by a set of paddles and electrically heated to 450°. The various reaction products were separated, as far as possible, in a low-temperature fractional-distillation apparatus of the type described by Booth and Bozarth (*Ind. Eng. Chem.*, 1937, **29**, 470) and Booth and McNabney (*ibid., Anal.*, 1944, **16**, 131), in which the head of the column is automatically cooled by small squirts of liquid oxygen to such a temperature as to maintain a pressure of one atmosphere. Vapour pressures and m. p.s were determined in a Stock apparatus, temperatures being measured by suitable vapour-pressure thermometers and copper–constantan thermocouples standardised against the mercury, carbon dioxide, and liquid oxygen fixed points. Molecular weights of gases were measured by means of a quartz-fibre suspension gas-density balance of standard type with electromagnetic control. The balance beam contained a short (1 cm.) permanent magnet, and under the thermostat tank containing the balance was a large, flat solenoid consisting of about 10,000 turns of enamelled copper wire (S.W.G. 34) on a wood former.

Hydrogen cyanide. This was fluorinated by cobalt trifluoride at 200—250° in the presence of 2—3 volumes of nitrogen. Any hydrogen fluoride formed was removed by passing the reaction products over sodium fluoride before they were condensed in traps cooled in liquid oxygen. Numerous fractional distillations of the volatile product gave: (*a*) b. p. −129°, *M*, 88 (CF_4), (*b*) a white solid subliming at 1 atm., *M*, 80—90, which was not investigated, (*c*) b. p. −77·6° to −78·9°, *M*, 124—128 ($CF_4 + CF_3{\cdot}NF_2$), (*d*) b. p. −38·0° to −39·1°, *M*, 161—171, and (*e*) residues b. p. −38° to +30°. Fraction (*d*), on careful distillation was divided into three approximately equal sub-fractions boiling within 1·1°, of *M* 161, 168, and 171 in order of increasing b. p. The middle fraction on analysis had the composition $C_3N_3F_{9{\cdot}4}$ and probably consisted mainly of $C_3N_3F_9$.

Trifluoromethyl cyanide. This was similarly diluted with nitrogen and fluorinated with cobalt trifluoride. In one experiment 9·5 l. of the cyanide gave, on fractionation of the product, (*a*) 6·48 l., b. p. −79·1° to −76·2°, *M*, 132 (C_2F_6, b. p. −78·2°, *M*, 138), (*b*) 1·16 l., b. p. −35·7° to −34·3°, *M*, 172 (C_2F_5N requires *M*, 171), and (*c*) 21 c.c., b. p. −35° to +40°. Very little carbon tetrafluoride was formed. Fraction (*a*) was evidently mainly hexafluoroethane, though the low molecular weight indicated that some perfluoromethylamine may have been present. Fraction (*b*), *perfluoroethylamine*, was redistilled for analysis and vapour-pressure measurement [Found: F, 77·6; N, 8·0%; *M*, 172. C_2NF_7 requires F, 77·8; N, 8·2%; *M*, 171].

Analysis. Several attempts to analyse gases containing carbon, nitrogen, and fluorine by heating them in a sealed tube with metallic potassium resulted in explosions. The method finally adopted was to reflux potassium in a U-tube *in vacuo* until all gases had been pumped off, then to allow the weighed sample of gas to react in small doses with boiling potassium. Nitrogen was pumped off by a Toepler pump and measured in a gas burette, and fluoride and cyanide determined in the contents of the U-tube after cooling and decomposition with alcohol. Some of the nitrogen appeared as gas and the rest as cyanide.

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617. *Characterisation of Monoalkyl Ethers of Ethylene and Diethylene Glycols.*

By E. S. Lane.

The reagents hitherto proposed (Veraguth and Diehl, *J. Amer. Chem. Soc.*, 1940, **62**, 233; Seikel and Huntress, *ibid.*, 1941, **63**, 593; Manning and Mason, *ibid.*, 1940, **62**, 3136) for the characterisation of monoalkyl ethers of ethylene and diethylene glycols have not proved entirely satisfactory. It has now been found that the allophanates of these glycols are readily prepared and crystallised. Allophanates have previously been used for the characterisation of a variety of alcohols (Paul and Riobe, *Compt. rend.*, 1947, **224**, 474; Gaddis and Butz, *J. Amer. Chem. Soc.*, 1947, **69**, 117; Naves, *Helv. Chim. Acta*, 1946, **29**, 553, 1447; Karrer and Hoffmann, *ibid.*, 1940, **23**, 1126; Blohm and Becker, *J. Amer. Chem. Soc.*, 1950, **72**, 5342). The method of preparation used is based on that used by Werner and Gray (*Sci. Proc. Roy. Dublin Soc.*, 1946, **24**, 77; 1947, **24**, 209). Attention is drawn to Spielman, Barnes, and Close's modification (*J. Amer. Chem. Soc.* 1950, **72**, 2520), which is convenient when the required allophanate (*e.g.*, that of 2-phenoxyethanol) is sparingly soluble in water. The allophanate of 2-2′-methoxyethoxyethanol is low-melting.

Experimental.—M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss of Oxford.

2-*Methoxyethyl Allophanate.*—2-Methoxyethanol ("Methyl Cellosolve") (15·2 g.) and dioxan (150 ml.) were stirred together, and anhydrous sodium cyanate (39 g.) added portionwise during 2 hours, while a stream of dry hydrogen chloride was passed through the mixture. Solvent and acid were removed under reduced pressure, and the solid residue was extracted with ether. The extracted material (21 g.) was recrystallised (charcoal) from ether, to give 2-*methoxyethyl allophanate*, m. p. 163° (Found: C, 37·05; H, 6·6; N, 17·4. $C_5H_{10}O_4N_2$ requires C, 37·1; H, 6·2; N, 17·3%).

2-*Ethoxyethyl allophanate*, similarly prepared, had m. p. 143—145° (11·1 g. from 18 g. of alcohol) (Found: C, 41·4; H, 6·6; N, 15·7. $C_6H_{12}O_4N_2$ requires C, 41·0; H, 6·8; N, 15·9%).

2-*Butoxyethyl Allophanate.*—2-Butoxyethanol (12 g.) and benzene (100 ml.) were stirred together while anhydrous sodium cyanate (25 g.) was added portionwise during 2 hours and a stream of anhydrous hydrogen chloride was passed in. The reaction mixture was evaporated to dryness. The residue (15·2 g.) was insoluble in water but easily soluble in methanol. Recrystallised from 9 : 1 water–methanol, it gave the *allophanate* as soft colourless crystals, m. p. 118° (Found: C, 47·2; H, 7·7; N, 13·5. $C_8H_{16}O_4N_2$ requires C, 47·1; H, 7·85; N, 13·7%).

2-*Phenoxyethyl Allophanate.*—2-Phenoxyethanol (13·8 g.) and glacial acetic acid (100 ml.) were stirred together while anhydrous sodium cyanate (19·5 g.) was added portionwise during 2 hours. The reaction mixture was stirred at room temperature for a further 2 hours, then poured into water, and the insoluble *allophanate* filtered off. It recrystallised from ethylene glycol monoacetate as colourless crystals, m. p. 219—220° (4·3 g.) (Found: C, 53·5; H, 5·3; N, 12·5. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%).

2-2′-*Methoxyethoxyethyl Allophanate.*—Prepared as above in dioxan, this was a slightly discoloured semi-solid material which could not be recrystallised owing to its excessive solubility.

2-2′-*Ethoxyethoxyethyl Allophanate.*—Prepared in dioxan (3 hours), this *allophanate* had m. p. 102—104° (Found: C, 43·7; H, 7·15; N, 12·9. $C_8H_{16}O_5N_2$ requires C, 43·7; H, 7·3; N, 12·7%).

2-2′-*Butoxyethoxyethyl Allophanate.*—2-2′-Butoxyethoxyethanol (16 g.) and benzene (100 ml.) were stirred together while anhydrous sodium cyanate (20 g.) was added portionwise during 1 hour and a stream of dry hydrogen chloride was passed through the mixture. The reaction mixture was heated (to remove acid) and filtered through sintered glass, and the filtrate evaporated. The residue was extracted with acetone, the solution filtered, and the filtrate evaporated to dryness. The solid (16·9 g.) was easily soluble in solvents but not in cold water. Recrystallisation from aqueous acetone gave the *allophanate*, m. p. 88° (Found: C, 48·5; H, 8·2; N, 11·0. $C_{10}H_{20}O_5N_2$ requires C, 48·4; H, 8·1; N, 11·3%).

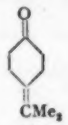
The author is indebted to The Director, Atomic Energy Research Establishment, for permission to publish this note.

A.E.R.E., Harwell, near Didcot, Berks. [*Received, April 4th*, 1951.]

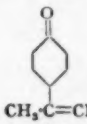
618. *The Preparation of* 4-iso*Propylidenecyclohexanone and its Derivatives.*

By K. G. Lewis.

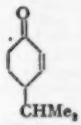
Recently Frank and McPherson (*J. Amer. Chem. Soc.*, 1949, **71**, 1387) prepared 4-*iso*propylidene*cyclo*hexanone (I) by distillation of γ-carboxy-γ-*iso*propenylpimelic acid with barium carbonate, proved its structure by ozonolysis to acetone and *cyclo*hexane-1 : 4-dione and by its conversion into γ-terpineol, and characterised it by means of a semicarbazone and a 2 : 4-dinitrophenylhydrazone. The last derivative, prepared in hot alcoholic hydrochloric acid, was orange which was unexpectedly dark in view of the non-conjugation of the carbonyl group and the ethylenic bond. It was also found that a Thorpe reaction, expected to yield (I), gave a substance which yielded the same 2 : 4-dinitrophenylhydrazone but a different semicarbazone. Frank and McPherson suggested the presence, in the second ketone, of some of the 4-*iso*propenyl isomer (II).



(I.)



(II.)



(III.)

The present author has found the same 2 : 4-dinitrophenylhydrazone to be formed from 4-*iso*propyl*cyclo*hex-2-enone (III). The discrepancies are resolved by recollecting the effect of strong acid on the unconjugated system (I). Formation of the hydrazone in hot acid, as practised by Frank and McPherson, gives the derivative of (III) from either (I) or (III); in the cold (cf. Birch, *J.*, 1946, 595), (I) gives a different 2 : 4-dinitrophenylhydrazone with the expected properties. The Thorpe reaction referred to above involves final hydrolysis with hot acid for 6 hours : Frank and McPherson's second ketone was therefore (III). The difference of the semicarbazones is thus explained. The identities of the dinitrophenylhydrazones have been confirmed by absorption spectra.

Experimental.—(M. p.s are uncorrected.)

4-iso*Propylidene*cyclo*hexanone*. This was prepared as recorded by Frank and McPherson (*loc. cit.*) and had b. p. 92—94°/13 mm., n_D^{23} 1·4819.

(*a*) The 2 : 4-dinitrophenylhydrazone, prepared according to Shriner and Fuson ("The Systematic Identification of Organic Compounds," John Wiley & Sons, New York, 2nd edn. 1940, p. 143), yielded deep orange-red plates, m. p. 132—134°, from alcohol. The mixed m. p. with authentic (±)-4-*iso*propyl*cyclo*hex-2-enone 2 : 4-dinitrophenylhydrazone (m. p. 136°) was 134—136°. The absorption max. in alcohol was at 3760 Å (ε 28,600).

(*b*) The ketone (0·5 g.) in alcohol (10 ml.) was added to 2 : 4-dinitrophenylhydrazine (0·5 g.) in alcohol (5 ml.) and concentrated sulphuric acid (0·5 ml.) and the mixture was kept cool. The resulting 2 : 4-dinitrophenylhydrazone was filtered off, washed with 5% sodium carbonate and water, and crystallised as golden-yellow plates, m. p. 122—124°, from alcohol. The absorption max. in alcohol was at 3650 Å (ε 22,500).

(*c*) The semicarbazone had m. p. 196—198° (from 90% alcohol), depressed when mixed with (±)-4-*iso*propyl*cyclo*hex-2-enone semicarbazone, m. p. 190—192°.

(±)-4-iso*Propyl*cyclo*hex-2-enone*. This was prepared by the racemisation of natural (−)-4-*iso*propyl*cyclo*hex-2-enone (cryptone) by Gillespie and Macbeth's method (*J.*, 1939, 1531). The 2 : 4-dinitrophenylhydrazone, deep orange-red plates, had m. p. 136° (from alcohol) (Gillespie and Macbeth record m. p. 130—131°; Birch, *loc. cit.*, gives m. p. 135—136°). The absorption max. in alcohol was at 3760 Å (ε 29,300). The semicarbazone had m. p. 190—192° (from 90% alcohol) (Gillespie and Macbeth record m. p. 188°).

The author thanks Professor A. K. Macbeth, of the University of Adelaide, and Mr. P. A. Berry for the sample of (−)-4-*iso*propyl*cyclo*hex-2-enone, also Mr. J. Ferguson, of the Chemistry Department, University of Sydney, for determination of the ultra-violet absorption spectra, and the Commonwealth Science Research Fund for financial assistance.

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619. *Paper Chromatography of the Cardiac Glycosides.*

By C. H. Hassall and S. L. Martin.

The recent publication by Schindler and Reichstein (*Helv. Chim. Acta*, 1951, **34**, 108) of a method for paper chromatography of cardiac glycosides utilising a stationary phase of formamide and various combinations of benzene and chloroform prompts us to describe now the results of our investigations using different procedures. As did the Swiss workers we found considerable variation in the behaviour of different glycosides. However, by using a variety of solvent mixtures, it has been possible to apply the technique to the separation and identification of the cardiac glycosides which have been investigated.

$100 \times R_F$ *Values of cardiac glycosides.*[1,2]

Solvent	Digilanid A		Digilanid B		Digilanid C		Digitoxin		Digoxin		Urechitoxin		Convallotoxin	
	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}
Ethyl acetate–water	52	36	0	—	0	—	94	92	86	68	85	82	36	31
Ethyl acetate–water [3]	74	62	0	—	0	—	87	82	0	—	80	74	36	21
Ethyl acetate–2·55N-aqueous sodium benzoate	0	—	28	27	0,11	0,6	0,91	0,88	0,80	0,67	0,46	0,44	0,24	0,13
Water–ethyl acetate	0·5	0·4	0·7	0·6	1·1	1	0	—	0·8	0·7	84	78	70	68
2·55N-Sodium benzoate–ethyl acetate	95	91	95	88	94	84	95	94	97	94	96	94	97	94
0·286N-Sodium benzoate–ethyl acetate	76	66	87	85	85,0·4	78,0·3	0	—	0·9	0·8	86	84	87	85
n-Butyl alcohol–water	87	82	76	74	82	78	93	90	88	86	76	72	66	62
n-Butyl alcohol–water [3]	92	89	92	87	96	93	95	88	96	92	81	75	73	63
Water–*n*-butyl alcohol	22	11	0	—	55	51	4·3	3·6	20	10	30	16	68	62
Ethyl oxalate–water	43	40	0	—	0	—	87	86	0·7	0·6	98	96	21	15
Water–ethyl oxalate	77	73	76	72	71	67	73	66	71	68	79	76	79	77
Ethyl methyl ketone–water	79	56	93	88	55	43	79	56	72	66	89	79	96	91
Water–ethyl methyl ketone	83	80	93	90	94	93	70	60	74	57	89	86	94	89
Water–ethyl methyl ketone [3]	95	92	87	84	98	97	95	92	98	96	97	94	90	88
Chloroform–water	0,39	0,20	0,13	0,7	0,6	0,3·4	0,73	0,64	0,46	0,36	0,62	0,44	0,5	0,2·8
Chloroform–water [3]	0,31	0,15	0	—	0,4·6	0,3·1	0,65	0,60	0,52	0,37	0,59	0,53	0,5	0,2·5

[1] With all combinations of solvent studied R_F value for gitoxin = 0·0. [2] The solvent front moved 20—30 cm. [3] Temp. 12°; in all other cases 34·5° ± 0·5°.

The table summarises the R_F values obtained with the representative series of glycosides studied. R_F values were calculated by using the front (R_{FF}) and centre (R_{FC}) of spots as reference points. They give an indication of the degree of longitudinal spread. In preliminary experiments, it was found that careful control of temperature was generally necessary for satisfactory results. In particular instances, *e.g.*, digoxin, digitoxin, it was possible to vary R_F values to obtain a better separation of constituents of a mixture by utilising this temperature effect. When good equilibrium conditions were maintained, there was normally satisfactory agreement between R_F values obtained in different experiments at a given temperature. In the two cases where significant variation between replicates occurred (digoxin, digilanid A) there was better agreement between R_{FF} than between R_{FC} values.

When ethyl acetate–sodium benzoate–water was used, two spots were obtained with single starting compounds. This also occurred with chloroform–water for all cases except gitoxin. Similar effects have been described elsewhere (Partridge, *Biochem. J.*, 1947, **42**, 244; Peterson and Reinecke, *J. Amer. Chem. Soc.*, 1950, **72**, 3598). The evidence suggests that this result may arise from the formation of artefacts in the course of chromatography.

As the table of R_F values indicates, all the glycosides investigated may be identified by this procedure when suitable solvents are employed. Technical difficulties are frequently encountered in the cardiac glycoside series in the separation of individuals on a preparative scale by the standard procedures of crystallisation, fractional elution chromatography, or partition. It appears likely that the chromatopile procedure (Mitchell and Haskins, *Science*, 1949, **110**, 278) could be applied with advantage to such cases when indications obtained from paper-strip chromatography are favourable; as an example, this method has been applied successfully to the separation of the digitalis glycosides gitoxin, digitoxin, and digoxin.

Experimental.—Apparatus. A small-scale modification of the standard pattern of apparatus used for descending paper chromatography has been employed. Four strips of filter paper (2 × 45 cm., Whatman No. 1), weighted at the free end with paper clips, were supported by the top segment (2·5 × 2·5

cm.) of a movable glass-rod frame with the other ends placed in a glass cup (2 × 3 cm.) fixed to the frame centrally below the top segment. The mounted frame was placed in a glass cylinder (45 × 7 cm.) permanently closed at the bottom and containing both liquid phases (in separate containers). The cylinder was closed by a large stopper carrying a small stoppered tube through which solvent could be introduced into the solvent cup.

Large-scale runs carried out with a stainless-steel tank similar to that described by Woiwod (*J. Gen. Bact.*, 1949, **3**, 312) gave R_F values which in some cases were consistently slightly higher than those obtained with the smaller apparatus and recorded in the table above.

Procedure. Both forms of apparatus were maintained at 34·5° ± 0·5° in an air thermostat. The glycoside solutions used were 1% (w/v) in methyl alcohol or methyl alcohol–chloroform. Normally two drops of solution (40—60 μg.) were applied with a micropipette giving a spot of approx. 0·3-cm. radius. The chromatography was carried out in a manner similar to that described by Jermyn and Isherwood (*Biochem. J.*, 1949, **44**, 402). The solvent front was allowed to move 20—30 cm. in the small apparatus and up to 50 cm. in the large one. The time required varied with the solvent from 1 to 10 hours.

The location of the spots was indicated by lightly spraying the dry papers with aqueous 5·5N-potassium hydroxide and then with 2% *m*-dinitrobenzene in ethyl alcohol (Raymond, *Analyst*, 1939, **64**, 113; Marlow, *J. Biol. Chem.*, 1950, **183**, 167). When necessary the light blue colours obtained were intensified by spraying again with aqueous potassium hydroxide. In the case of gitoxin, only faint colours are obtained and the test is not always reliable. The position of the gitoxin may be confirmed by applying the Keller–Kiliani reagent to extracts of strip sections or by utilising the colour obtained with hydrogen chloride (Mesnard and Deveze, *Bull. Trav. Soc. pharm. Bordeaux*, 1950, **88**, 109).

The length of the spot increases with the amount of glycoside used although in the cases studied the position of the spot front does not show significant variation due to this factor. It is probable that this contributes to the better reproducibility shown by R_{PP} values in a series of experiments in which there was some variation in the amount of glycoside used (40—60 μg.).

Chromatopile chromatography. A mixture of gitoxin (20 mg.), digitoxin (30 mg.), and digoxin (20 mg.) was applied in chloroform–methanol to three filter papers (Whatman No. 1, 11 cm.) which were introduced into the top of a pile compressed to 18·7 cm. in the form of the commercially available chromatopile apparatus (Mitchell and Haskins, *loc. cit.*). Chromatography was carried out by the standard procedure at 34·5° with ethyl acetate–water. The apparatus was allowed to come to equilibrium overnight in an enclosed vessel containing both phases of the solvent mixture. Qualitative examination of sections of the papers at the end of the experiment indicated R_F values for the individual glycosides similar to those obtained on paper strips. The glycosides concentrated on the periphery of the papers. The identity and purity of the three constituents separated in this way was confirmed by extraction from the paper at different locations, recrystallisation, and comparison on paper-strip chromatograms with pure products.

We are indebted to Roche Products Ltd., Prof. A. Stoll, and Burroughs Wellcome & Co. (U.S.A.) Inc. for samples of authentic glycosides, and to Roche Products Ltd. and the Chemical Society for grants.

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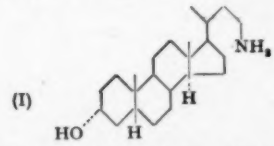
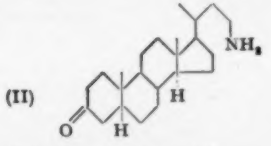
620. *Basic Derivatives of Steroids. 23-Amino-3α-hydroxy- and 23-Amino-3-keto-norcholane.*

By MARJORIE L. HILTON and M. WEBB.

THE synthesis, from cholic and deoxycholic acids, of certain basic derivatives of norcholane which possessed bacteriostatic properties was recorded in a previous paper (James, Smith, Stacey, and Webb, *J.*, 1946, 665). This work has now been extended to the preparation from lithocholic acid of 23-amino-3α-hydroxy- (I) and 23-amino-3-keto-norcholane (II) by decom-





position of the azides derived from the hydrazide and hydrazono-hydrazide respectively (cf. Caldwell, *J. Amer. Chem. Soc.*, 1938, **60**, 991; 1939, **61**, 3584).

The bacteriostatic concentrations of the hydrochlorides of (I) and (II) against *Staph. aureus* (Oxford, Strain D), determined by the serial dilution method in a glucose–broth medium (pH 7), were respectively 1 : 256,000 and 1 : 64,000 after 48 hours at 37°. Both compounds were inactive when tested against the Gram-negative organism *Aerobact. aerogenes*.

Experimental.—Lithocholic acid. Methyl cholate was converted into methyl 3α-(β-carboxypropionoxy)-7 : 12-diketocholanate which was then reduced in 5-g. quantities to lithocholic acid, m. p. 184° (Heusser and Wuthier, *Helv. Chim. Acta*, 1947, **30**, 2165).

Lithocholylhydrazine. A mixture of methyl lithocholate (1·95 g.) and absolute hydrazine hydrate (25 ml.) was boiled under reflux for 5 hours. The excess hydrazine hydrate was then removed by evaporation under reduced pressure and the solid residue dried *in vacuo* over concentrated sulphuric acid. Crystallisation from ethanol, gave *lithocholylhydrazine* (1·5 g.) as white needles, m. p. 214—217° (sintering at 211°), $[\alpha]_D^{18}$ +36° (*c*, 1·0 in ethanol) (Found : C, 73·4; H, 10·9; N, 7·0. $C_{24}H_{42}O_2N_2$ requires C, 73·8; H, 10·8; N, 7·2%).

23-*Amino*-3α-*hydroxynorcholane hydrochloride.*—A solution of sodium nitrite (0·4 g.) in water (5 ml.) was added slowly with stirring to a solution of the hydrazide (1·5 g.) in 5N-hydrochloric acid (50 ml.) and acetic acid (80 ml.) at 0° to −5°, until excess of nitrous acid was detected (starch–iodide paper). After 30 minutes, the suspension was poured into ice-water (200 ml.), and the azide collected by filtration, washed with ice-water, and transferred, while still moist, into acetic acid (50 ml.). The suspension was heated on a steam-bath until the solid had dissolved and the evolution of gases had ceased (*ca.* 2 hours). The solution was cooled to 0° and made alkaline to litmus with sodium hydroxide, and the precipitated amine collected (centrifuge), washed with ice-water, and dried (P_2O_5–NaOH). Dry hydrogen chloride was passed through a solution of the crude amine in dry chloroform until no further precipitation of the hydrochloride occurred. The supernatant liquid was decanted and the gelatinous precipitate triturated with acetone until solid. Crystallisation from ethanol–acetone (1 : 3) gave 23-*amino*-3α-*hydroxynorcholane hydrochloride* (0·6 g.) as needles, m. p. >300° (decomp.), $[\alpha]_D^{19}$ +37·5° (*c*, 1·02 in ethanol) (Found, after drying at 180° : C, 72·1; H, 10·6; N, 3·7. $C_{23}H_{42}ONCl$ requires C, 71·9; H, 10·9; N, 3·65%).

3-*Ketocholanic acid.*—Lithocholic acid was oxidized with chromic acid according to Wieland and Dane's method (*Z. physiol. Chem.*, 1932, **212**, 48). The reaction product was poured into water, and the resulting emulsion extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated *in vacuo*. The residual syrup was triturated with methanol until solid. Recrystallisation from methanol afforded 3-ketocholanic acid (1·45 g.; m. p. 139°).

Hydrazone of 3-*ketocholanylhydrazine.* A solution of methyl 3-ketocholanate (1·35 g.) in absolute ethanol–hydrazine hydrate (25 ml. each) was boiled under reflux for 12 hours. The solution was filtered, evaporated under reduced pressure, and dried *in vacuo* over concentrated sulphuric acid. Trituration of the syrup with ethanol yielded a gelatinous solid which hardened on treatment with ether, to give 3-ketocholanylhydrazine hydrazone (1·0 g.) as a white amorphous powder.

23-*Amino*-3-*ketonorcholane hydrochloride.* Sodium nitrite (0·5 g.) in water (5 ml.) was added slowly with stirring to a solution of the foregoing hydrazone (905 mg.) in 5N-hydrochloric acid (25 ml.)–acetic acid (80 ml.) at 0°, until excess of nitrous acid was detected (starch–iodide paper). After 30 minutes at 0° the solution was poured into ice-water (200 ml.), and the precipitated azide collected, washed with ice-water, and transferred into glacial acetic acid (30 ml.). The suspension was heated on a steam-bath until evolution of gases had ceased (1½ hours); the resulting solution was cooled to 0° and neutralised with sodium hydroxide. The emulsion thus obtained was extracted with chloroform and the extract washed with water and dried ($MgSO_4$). Dry hydrogen chloride was passed for 10 minutes through the cooled solution which was then evaporated to dryness under reduced pressure at room temperature. A white solid remained which was triturated with acetone, washed twice with acetone, and collected (centrifuge). Crystallisation from ethanol–light petroleum and recrystallisation from acetone–water gave 23-*amino*-3-*ketonorcholane hydrochloride* as colourless needles (100 mg.), m. p. 236° (decomp.), $[\alpha]_D^{21}$ +54·7° (*c*, 1·13 in ethanol) (Found, after drying at 180° : C, 72·7; H, 10·0; N, 3·5. $C_{23}H_{40}ONCl$ requires C, 72·4; H, 10·5; N, 3·7%).

The authors thank Professor M. Stacey, F.R.S., for his interest in this work. One of them (M. L. H.) is indebted to the Department of Scientific and Industrial Research for a grant.

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[*Received, June 12th*, 1951.]

621. *The Preparation of Acid Anhydrides.*

By A. McGookin and H. Page.

It has been shown (Klinger and Schmitz, *Ber.*, 1891, **24**, 1271; 1276; Basse and Klinger, *Ber.*, 1898, **31**, 1217) that the action of sodium on acid chlorides in dry ether is abnormal and leads to esters of unsaturated glycols $RCO_2{\cdot}CR{:}CR{\cdot}O_2CR$. Vavoglis (*Ber.*, 1937, **70**, 2391) obtained ethyl benzoate from benzoyl chloride and zinc or iron in dry ether. Pearl, Evans, and Dehn (*J. Amer. Chem. Soc.*, 1938, **60**, 2478) produced a similar result by using sodium and ether but found that potassium in dry xylene gave the corresponding anhydride from benzoyl, succinoyl, or phthaloyl chlorides; evidently oxidation of a free radical occurs in this reaction; toluene-*p*-sulphonyl chloride yielded di-*p*-tolyl disulphone; no reference to the early work in this field is given.

Ralston and Selby (*J. Amer. Chem. Soc.*, 1939, **61**, 1019) extended the work of Klinger and his collaborators to higher fatty acid chlorides and obtained similar products.

No work appears to have been done on the action of metallic oxides on acid chlorides. Investigation showed that the reaction proceeds, as expected, according to the equation:

$$2R{\cdot}COCl + M_2O\ (M'O) \longrightarrow (R{\cdot}CO)_2O + 2MCl\ (M'Cl_2)$$

Silver and yellow mercuric oxides reacted readily; lime gave a poor yield of anhydride; and cupric oxide, although it caused a vigorous reaction, did not furnish a solid product. The reaction is improved by using an excess of the metallic oxide whereby all the acid chloride is removed, otherwise the final separation is difficult.

Experimental.—Benzoic anhydride. (1) Dry silver oxide (21 g.) was added in small amounts to benzoyl chloride (24·5 g.) with rapid stirring (mercury seal). The two-necked flask was cooled in ice. Much heat, causing white fumes, developed. When addition was complete, pure dry benzene (40 ml.) was added and the mixture was refluxed for 1 hour. After filtration the solvent was removed and the brown oily residue distilled in a vacuum, to remove benzoyl chloride. The solid residue (13 g.) was dissolved in ether, and the solution warmed with norite for ½ hour, filtered, and freed from the ether. Benzoic anhydride (9 g.), m. p. 41—42°, was obtained. Recrystallization from light petroleum (b. p. 60—80°) gave colourless needles, m. p. 42°. Hydrolysis furnished benzoic acid, m. p. 121°.

(2) Benzoyl chloride (24 g.) and dry benzene (20 ml.) were similarly treated with dry yellow mercuric oxide (21 g.), added slowly with stirring and cooling. Benzene (20 ml.) was then added and the mixture refluxed for ½ hour, then filtered, and the solvent removed. Benzoic anhydride (9 g.), m. p. 40—42°, remained. Extraction of the mercuric chloride with dry ether and recrystallization of the extract from light petroleum (b. p. 60—80°) gave colourless needles, m. p. 42° (2 g.). The anhydride, on hydrolysis, yielded benzoic acid, m. p. 121°.

(3) Benzoyl chloride (24·2 g.), benzene (20 ml.), and dry lime (10 g.) were refluxed for 4 hours. After filtration and removal of the benzene, colourless crystals (3 g.), m. p. 41—42°, of benzoic anhydride were obtained.

p-Toluic anhydride. (1) *p*-Toluoyl chloride (10 g.) in dry benzene (20 ml.) was added, with stirring, to dry silver oxide (10 g.) cooled in ice. After addition of benzene (20 ml.) and refluxing for 1 hour the silver chloride was filtered off, the solvent removed, and the residue (7·5 g.) recrystallized from light petroleum (b. p. 60—80°). Colourless needles (5 g.), m. p. 95°, of *p*-toluic anhydride separated. Hydrolysis gave *p*-toluic acid, m. p. 181°.

(2) *p*-Toluoyl chloride (15·6 g.) in dry benzene (20 ml.) was similarly run in to a flask containing a slight excess of dry yellow mercuric oxide. After similar treatment colourless crystals (5·7 g.), m. p. 95°, were obtained which were hydrolysed to *p*-toluic acid.

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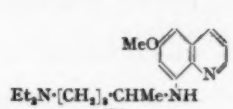
A Chemotherapeutic Search in Retrospect.

THE TILDEN LECTURE, DELIVERED AT THE ROYAL INSTITUTION, LONDON, ON JUNE 7TH, 1951, AND IN BANGOR ON NOVEMBER 23RD, 1950.

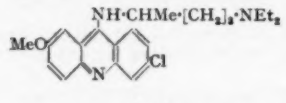
By F. L. ROSE, O.B.E., Ph.D., D.Sc., F.R.I.C.

A CHEMOTHERAPEUTIC search is a quest for a chemical substance having a specific use in medicine, and as such is an exercise in applied science, although its execution may call for a high degree of scientific ingenuity from both the chemist and the biologist. Nevertheless, the objective has to be kept constantly in view and the temptation to wander from the path that leads to it resisted. When the search was conducted under the stress of war, as was the case with the early stages of the attempts to discover new antimalarial agents here described, this outlook had to be adhered to ruthlessly, so that many interesting side-observations had to be disregarded at least temporarily. Only later, when the emergency was past, was it possible to go back and examine the field of endeavour at greater leisure. Such a course is particularly apt in the present circumstance since the emergence of a highly active agent of novel type has tended to focus attention on the particular sequence of events and substances immediately concerned in its evolution, with a consequent neglect of numerous earlier types, many of considerable therapeutic interest at the time, but which for one reason or another could not be improved upon, and had in consequence to make way for more fruitful leads. The purpose of this lecture is to rectify these omissions by providing a fuller account of the research as a whole. By way of introduction, it is proposed to give a historical account of the events leading up to the present endeavours.

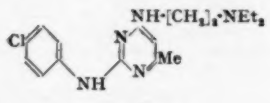
Although quinine has been recognised as a specific curative agent in malaria since its isolation from cinchona bark by Pelletier and Caventou in 1820, it is only within the last 25 years that its position has been challenged by the introduction of synthetic substitutes. The earlier misguided but in other ways significant attempts by Perkin to produce quinine by the oxidation of aniline being disregarded, the history of synthetic drugs goes back to the observation by Ehrlich and Guttman [1] in 1891 that methylene-blue possessed a certain amount of antimalarial action, and to the work of Skraup, Königs, Rabe, and others on the structure of the cinchona alkaloids. In Germany, Schulemann, Schönhöfer, and Wingler [2] utilised this knowledge, and by a series of steps arrived at Pamaquin (then called Plasmoquine) (I) first introduced clinically by Muhlens [3] without full disclosure of its constitution.



(I.)
Plasmoquine = pamaquin B.P.



(II.)
Atebrin = mepacrine B.P.



(III.)
" 2666."

In England, independently and more or less simultaneously, the main early attack on the preparation of synthetic antimalarials was carried out by Robinson, Kermack,[4] and their collaborators in co-operation with Keilin, by an arrangement with the Joint Chemotherapy Committee of the Medical Research Council and the Department of Scientific and Industrial Research. Here the important clues followed up were the constitution of quinine and the harmala alkaloids, and the later statement of the I.G. Farbenindustrie A.G. that Plasmoquine was the salt of an alkylamino-6-methoxyquinoline. The most active compounds were ultimately found, as with the latter, to be those carrying an alkylaminoalkylamino-grouping in position 8 of the quinoline nucleus. Before the War, related researches were also in progress in France under Fourneau, in Russia under Magidson, and in India under Brahmachari. The next important step forward was taken by the German workers in their exploitation of the pamaquin lead. Aminoalkylamino-groups had been introduced into many other heterocyclic systems including xanthens, azines, oxazines, thiazines, and acridines, but it was the last-

[1] Ehrlich and Guttman, *Berlin klin. Woch.*, 1891, **28**, 593.
[2] Schulemann, Schönhöfer, and Wingler, *Klin. Woch.*, 1932, **11**, 381.
[3] Muhlens, *Arch. Schiffs- u. Tropenhyg.*, 1926, **30**, Beiheft 3, 25.
[4] Robinson, Kermack, and co-workers, " Attempts to find New Antimalarials," Parts I—XXIX, *J.*, 1929 *et seq.*

named type only that provided drugs of special merit. Soon after the evaluation of pamaquin it was realised that this substance did not provide an adequate substitute for quinine, as it had no action on the asexual forms of malignant tertian malaria. In the course of an investigation of 10-aminoacridines, however, Mietzsch and Maus [5] finally succeeded in evolving a compound active against the schizonts of all three types of human malaria. The drug was first called Plasmoquine E, then Erion, and later Atebrin (now known in this country as mepacrine) (II). Then followed extensive researches on this class of compound, not only in Germany but again in Russia by Magidson and his collaborators who provided much useful information relating structure with activity, and in England by Clemo, Kermack, and workers in the D.S.I.R. laboratories. No significant improvement, however, was made.

Despite higher antimalarial potency, mepacrine had achieved little more before 1939 than having come to be regarded as a possible substitute for quinine, but with the imminence of war this aspect assumed more than ordinary importance, so much so that both pamaquin and mepacrine were included in a list of essential drugs proposed in 1938 for process study by the Association of British Chemical Manufacturers. In these laboratories the task of putting this proposal into effect was initially entrusted to the late Dr. F. H. S. Curd, and by September 1939 pilot-plant production of mepacrine had begun, soon afterwards to be transferred to full manufacture on a scale sufficient to make a considerable contribution to the needs of the armed forces operating in malarious areas. Meanwhile, the plans for novel research had been maturing and these became part of the national war-time scheme organised a little later by the Medical Research Council, and linked through that body with the efforts of the American National Research Council. Under the auspices of the former, prominent scientists in the universities were invited to take part in the researches, and there began a long period of happy and eventually fruitful collaboration. To illustrate this point it might be mentioned that of the 40 authors that have contributed to nearly 50 papers describing the chemical aspects of these labours, exactly one-half conducted their studies in academic laboratories. Further, some 1700 compounds were prepared and examined in the period up to 1947, of which nearly one-third showed highly significant effect in experimental infections. Clearly, a detailed review of an effort of such magnitude is beyond the scope of the present contribution. Therefore, items have been selected for discussion, not so much on the basis of the clinical utility of the substances concerned, but as illustrative of the apparent diversity of chemical types which provided activity in the experimental stages, and their relation to those which did not. In this, the Lecturer presumes to speak, not only for his own colleagues, but for all who contributed to the concerted effort.

At the outset it had been decided to attempt to break away from the quinoline and acridine types that had been so extensively exploited by earlier workers in this field, and in consequence a lengthy period of barren endeavour was expected. It was a more than pleasant surprise therefore to find activity in the third or fourth of the seemingly entirely novel structures that were prepared. In retrospect, it is clear that with the particular working hypothesis evolved as a guide to new synthesis, activity could hardly have been missed even at the earliest stages of the research. The principles for devising these particular drugs were compounded from known active substances, notably mepacrine and the sulphapyrimidines. The former was regarded as made up of methoxyl- and chlorine-substituted benzene nuclei associated with a potentially tautomeric amino-heterocyclic system and a " basic side chain " of the alkylaminoalkyl type. The latter, more especially a dimethyl derivative (" Sulphamezathine " : sulphadimidine B.P.C.), had just been shown to be active in human malaria, a property apparently to be associated with the pyrimidine ring, and moreover, the recent introduction of this " sulpha " drug into clinical practice as an antibacterial agent [6] and the variations made in its structure,[7, 8] had given a useful familiarity with the chemistry of pyrimidine. In consequence, and additionally because of the known biological importance of this ring system, it was decided to make it the central nucleus around which to array the " active " moieties deduced by consideration of the mepacrine molecule. The compound " 2666 " (III) was the first to show activity against chick malaria (*P. gallinaceum*) in the biological assays conducted throughout by Dr. D. G. Davey, and although clinical test proved abortive, it provided one of the important leads from which so much of the subsequent success was to follow.[9]

[5] Mietzsch and Maus, *Klin. Woch.*, 1933, **12**, 1276.
[6] Rose, Martin, and Bevan, *J. Pharmacol.*, 1943, **77**, 127.
[7] Rose and Swain, *J.*, 1945, 689.
[8] Rose and Tuey, *J.*, 1946, 81. [9] Curd and Rose, *J.*, 1946, 343.

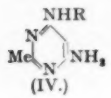
Parallel with this investigation, a cognate series of researches on pyrimidine derivatives was commenced by Todd and his group,[10] who elected to study compounds similar to those mentioned above, but without the aryl substituent. Here again, activity in the experimental infection was encountered at an early stage, providing an additional lead, although the greater relative toxicity of the non-aromatic preparations was ultimately to debar them from clinical consideration.

From this point and for some time to come, the scheme for development was almost automatic, and two broad lines were followed. In the first, the pyrimidine nucleus was retained and subjected to further embellishment, and in the second, the aniline and basic side-chain residues were substituted into yet other heterocyclic systems. As the researches progressed, the more promising leads were still further sub-divided, until some 40 distinct chemical classes were eventually examined, together with many more of which only a few examples each were made.

The sections which now follow outline the chemistry of some of the substances prepared, and provide comment on therapeutic effect. General discussion on structure in relation to activity appears later. To facilitate appreciation of the sequence of events, the various types have been grouped more or less on the basis of their conception, but not necessarily in exact chronological order since many were under investigation simultaneously.

In most of the structures formulated below the so-called basic side chain, usually the simplest dialkylaminoalkylamino-groups, such as 2-diethylaminoethylamino- or 3-diethylaminopropylamino-, figure prominently, although much more complex types were also examined. No attempt has been made to formulate all the variations made, although specific points are dealt with in the final discussion. Instead, the occurrence of such a side chain is denoted by the symbol –NHR, with R defined more fully if occasion demands.

Pyrimidines.—(a) *Non-aryl pyrimidine derivatives.*[10, 11] As a matter of deliberate policy, the first preparations of this type contained the pyrimidine nucleus as lightly substituted as possible,[10] and included the simple derivatives (IV)—(IX). These substances were prepared for the most part from the appropriate chloropyrimidines by direct reaction with the side-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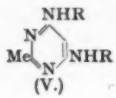
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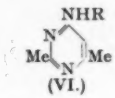
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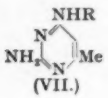
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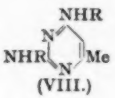
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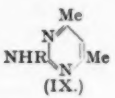
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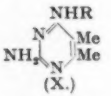
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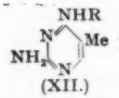
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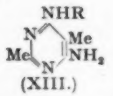
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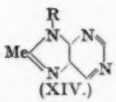

(XIV.)

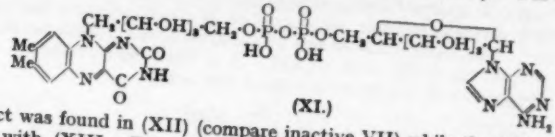
chain amine. Not one compound in this series was active. Antimalarial activity was first encountered, however, when a 5-methyl group was introduced into type (VII) giving (X), although most of the compounds prepared were also highly toxic. Omission of the 2-amino-group, or its replacement by methyl, *i.e.*, to give the 5-methyl compound corresponding to (VI), reduced activity very markedly without materially affecting toxicity, while replacement of the 2-amino-group by a second dialkylaminoalkylamino-group completely destroyed therapeutic effect.

These findings naturally led to a thorough study [11] of the effect of varying the nature of the basic side chain and the substituents at positions 5 and 6. At this stage consideration was given to the possible mode of action of the 5-substituted compounds so that this further development could be as rational as possible. Since an antagonism for riboflavin had already been proposed and demonstrated experimentally by use of *Lactobacillus casei* to explain the therapeutic action of the arylamino-pyrimidines described below, it seemed likely that the simpler compounds might in their turn act through interference with the structurally related purine component of a riboflavin–adenine dinucleotide (XI), either with synthesis or function.

It was further postulated on formal grounds that pyrimidine derivatives substituted in the 4 : 5-position might present optimum conditions for such an antagonism, in particular those bearing a side chain of moderate size in position 4 (=6) corresponding to that of the carbo-

[10] Hull, Lovell, Openshaw, Payman, and Todd, *J.*, 1946, 357.
[11] Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41.

hydrate residue in adenosine, and it was in fact subsequently observed that only those substances fulfilling these conditions showed marked antimalarial activity. For instance, marked

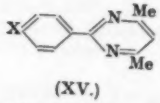


(XI.)

therapeutic effect was found in (XII) (compare inactive VII) while the highest activity in this series occurred with (XIII; R = $[CH_2]_3 \cdot NEt_2$) (compare inactive IV). Substituents other than methyl in position 5 also promoted activity, including ethyl, benzyl, phenoxy-, and ring structures such as that provided by 5 : 6-*cyclo*hexeno-. Curiously enough, the related purines themselves, for example (XIV), and others prepared later, have been entirely devoid of positive effect.

(b) *Aryl-substituted pyrimidines.* This type included the earliest compounds made in this research, and because of this, and a capacity for almost unlimited variation, it has received by far the fullest exploitation of any chemical class. For convenience in discussion, the preparations have been sub-divided into pyrimidines carrying a direct aryl or arylamino-substituent, and others in which the aryl residue is variously connected to the heterocyclic system, for example, through guanidino-, amidino-, ureido-, thioureido-, ether, and thio-ether linkages.

(i) Aryl- and arylamino-pyrimidines.[9, 12-16] Compound (XV; X = H) perhaps deserves special note as the first preparation of the campaign.[9] Its relation to sulphadimethylpyrimidine



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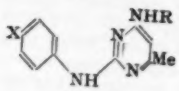
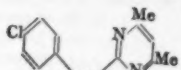


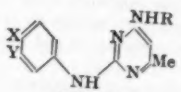
(XVI.)



(XVII.)

(sulphadimidine B.P.) is obvious. It was, however, inactive like the second substance (XV; X = OMe) and a slightly later preparation (XV; X = Cl). The introduction of the concept of tautomeric possibility and the need for marked basicity led to (XVI; X = Cl or OMe) and the immediate observation of antimalarial activity in the chick. The influence of the basic side chain was stressed by the inactivity of the parent amine (XVI; R = H), the corresponding hydroxy-derivative, and (XVII).

Early developmental work based on the novel (XVI) was necessarily somewhat empirical, but even so, it was influenced to no small extent by speculations regarding mode of action. The notion of riboflavin antagonism was postulated almost immediately, and indeed some two years before it was demonstrated experimentally with respect to the growth of *Lactobacillus*



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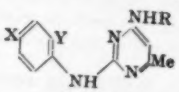

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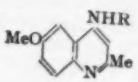


(XX.)

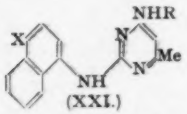
casei. This hypothesis [13] led, for example, to the preparation of compounds of type (XVIII) substituted in the 3 : 4-positions in the benzene ring (compare XI).

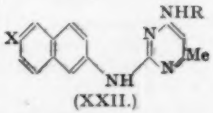
A wide variety of *p*-substituents introduced into (XVI) gave positive activity including, in addition to those already mentioned, bromo, iodo, fluoro, nitro, cyano, phenyl, dimethylamino, and carbomethoxy. The parent anilino-derivative (XVI; X = H) was inactive. In general, *m*- or *o*-substitution gave activity of a reduced order. 3 : 4-Substitution did not lead to enhanced effect, nor did 2 : 4-substitution (XIX; Y = Me or Cl) where it was expected

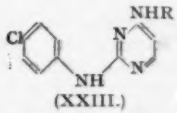
[13] Curd, Davis, and Rose, *J.*, 1946, 351.
[14] Curd, Raison, and Rose, *J.*, 1946, 366.
[14a] Magidson and Rubtsov, *J. Gen. Chem. Russia*, 1937, **7**, 1896.
[15] Curd, Davis, Owen, Rose, and Tuey, *J.*, 1946, 370.
[16] *Idem, ibid.*, p. 720.
[17] Basford, Curd, and Rose, *J.*, 1946, 713.
[18] Basford, Curd, Hoggarth, and Rose, *J.*, 1947, 1354.

that the *o*-substituent would provide a structure more nearly equivalent to the *iso*alloxazine system of riboflavin. The 2 : 5-dichloro-analogue was completely inactive.

An additional form of disubstitution, equivalent to 2 : 3- and 3 : 4-respectively, was provided by preparation and examination of a number of naphthylamine derivatives of types (XXI) and (XXII).[13] The latter included one of the most active compounds in the arylaminopyrimidine class (XXII; X = Br), and (XXII; X = OMe) was almost as effective. The α-naphthylamine derivatives (XXI) were very much less active.


(XXI.)

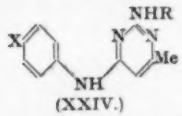

(XXII.)


(XXIII.)

The need for the 6-methyl group in the pyrimidine nucleus was next investigated.[14] Its occurrence in many of the early structures was associated with the greater accessibility of the compounds so substituted, but clearly its intrinsic importance had to be assessed, particularly since amongst the quinoline antimalarial agents is was known that the introduction of methyl adjacent to the heterocyclic nitrogen atom, as in (XX), had a dystherapeutic influence.[14a] In this series, however, its omission, giving (XXIII), was attended by lowered activity. Activity persisted with phenyl in position 6 but much reduced, while chlorine and methoxyl derivatives were inactive.

With regard to substitution in position 5, we had before us knowledge of the profound effect produced in the non-aryl type.[14] It appeared possible that enhancement of therapeutic effect might again result through the consequent hypothetical widening of the range of antagonism to include enzyme systems based on purine nucleosides. This result was not achieved, however, since groups such as methyl, ethyl, propyl, butyl, benzyl, phenyl, phenoxy-, and bromine, and ring closure to 5 : 6-*cyclo*penteno- or -*cyclo*hexeno-, all reduced activity, the reduction being roughly proportional to the mass of the substituent.

All the above substances carried the aryl group in position 2 of the pyrimidine ring, and the basic group at 4. The next major modification was the transposition of these substituents to give the isomeric (XXIV).[15] Activity again resulted and the variations already applied to (XVI) were made.[16] In general, very similar effects were observed. For example, chlorine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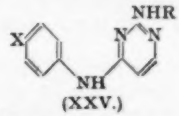
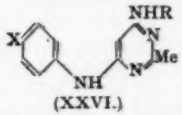
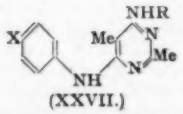
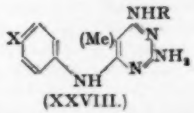

(XXV.)

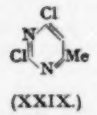

(XXVI.)

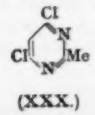
in the phenyl residue could be replaced by nitro- or cyano- to give equally active, if not more active, agents. The *p*-anisidino-derivatives were inactive, however, as were also the 3′ : 4′-dichloroanilino-compounds. The naphthylamines were very much less active in this series. Substitution in position 5 of the pyrimidine ring reduced activity somewhat, as did replacement of 6-methyl by hydrogen (XXV).

Finally, the third isomeric type (XXVI) was examined. The usual variations of *p*-substituent and basic side chain were made [17] but without revealing more than a trace of antimalarial action among the first dozen compounds, and that at doses which killed a proportion


(XXVII.)

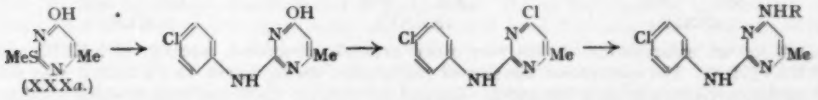

(XXVIII.)


(XXIX.)


(XXX.)

of the test birds. The influence of a substituent in position 5 of pyrimidine in the earlier type (X) (compare VII) being borne in mind, similar substitution was made in (XXVI) to give, not only (XXVII), but the analogous 5-ethyl, -amino-, and -phenyl derivatives.[18] Likewise the methyl group in position 2 of (XXVI) and (XXVII) was replaced by higher alkyl, by phenyl, and by amino- to give, in the last instance, compounds (XXVIII) derived from 2 : 4 : 6-triaminopyrimidine. Of a total of 40 such preparations, however, only a few showed activity, and that marginal.

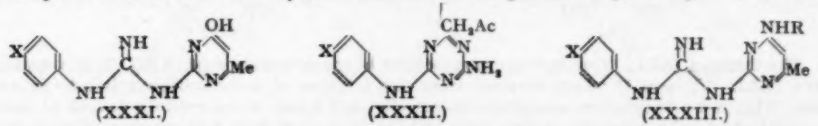
With regard to the synthesis of the three types of isomeric arylaminoalkylaminopyrimidines discussed above, the first step was to introduce one or other of the main amine substituents into the pyrimidine ring, by replacement for example of chloro- or methylthio-groups, leaving a second grouping, usually hydroxyl, to be then converted into chloro- by the action of phosphoryl chloride, and subsequently causing this to react with the second amine component, *e.g.*:



This stepwise production of, and reaction with, labile groupings, was found preferable to attempted reaction of the amine components with only one of the chlorine atoms in, *e.g.*, (XXIX) or (XXX), when mixtures either of isomers or of mono- and di-substitution products were frequently obtained, which were often extremely difficult to fractionate.

(ii) Aryl-guanidino-, -ureido-, -thioureido-, -oxy-, and -thio-pyrimidines.[19-23] The aryl derivatives of pyrimidine described above all had the aryl group linked to the heterocyclic system either directly or through amino-. Other methods of linkage required investigation and those based on ·NH·C(:NH)·NH·, ·NH·CO·NH·, ·NH·CS·NH·, ·O·, and ·S· were first examined. Of these, only the first three provided scope for the operation of tautomerism then being developed as a potentially significant feature governing antimalarial effect, and it seemed that the outcome of this section of the research would provide useful evidence for or against the hypothesis.

Access to the phenylguanidinopyrimidines was provided by a convenient reaction between aryldiguanides and β-keto-esters to give almost exclusively compounds, *e.g.*, of type (XXXI), accompanied in some instances by small amounts of the guanamine (XXXII).[19] Conversion



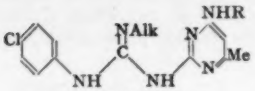
of the hydroxyl substituent into chloro-, followed by reaction with the second amine component, gave type (XXXIII). It was almost immediately apparent that this class provided a higher order of antimalarial activity at a lower level of general toxicity in experimental assays than the arylaminopyrimidines previously described, and it was one such preparation (XXXIII; X = Cl, R = CH_2·CH_2·NEt_2) that first showed useful clinical effect in man. A detailed investigation followed to determine optimal substitution in the molecule.[20] About 70 compounds were made of which 60 showed a significant degree of therapeutic effect. Since the parent (XXXIII; X = H) was quite active, it was possible to define approximately the relative influence of different substituents in the benzene ring. Potentiation was given by chlorine, fluorine, bromine, iodine, nitro-, cyano-, methylthio-, and phenyl in descending order of magnitude, optimum activity being usually associated with the *p*-position. *p*-Methyl or -methylsulphonyl was about as effective as hydrogen, but sulphonamido-, methoxyl, and dimethylamino- deactivated. Substituents in position 5 of the pyrimidine ring also had a dystherapeutic effect.

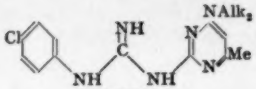
A further variation was the introduction of alkyl (*e.g.*, Me, Et, Bu) at the central nitrogen atom of the guanidine linkage to give type (XXXIV).[21] Activity still remained, though of a lower order than in the parent (XXXIII).

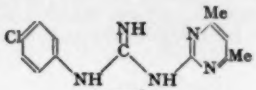
Because of the greater base strength associated with the arylguanidino-residue than with arylamino-, it was argued that it might be possible to omit or simplify the basic side chain and still retain activity. The related types (XXXV) and (XXXVI) were therefore made,[20] in the former the dialkylamino-group being diethylamino-, methyl*iso*propylamino-, or piperidino-. Both types did indeed provide quite a high degree of activity. It was also found that when

[19] Curd and Rose, *J.*, 1946, 362.
[20] Cliffe, Curd, Rose, and Scott, *J.*, 1948, 574.
[21] Crowther, Curd, and Rose, *J.*, 1948, 586.
[22] Ashworth, Crowther, Curd, and Rose, *J.*, 1948, 581.
[23] Curd, Davis, Hoggarth, and Rose, *J.*, 1947, 783.

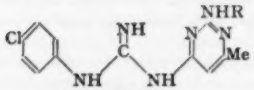
the alkyl groups in (XXXV) were both of the basic side chain type, an inactive compound resulted. The high therapeutic action of the 2-arylguanidinopyrimidines (XXXIII) clearly

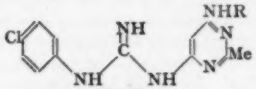

(XXXIV.)

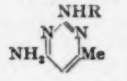

(XXXV.)

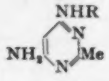

(XXXVI.)

called for an examination of the two other isomeric structures, namely, (XXXVII) and (XXXVIII).[21] The convenient method of preparation giving access to (XXXIII) was not, of course, applicable in these instances. Instead, an indirect route was used in which *p*-chlorophenyl *iso*thiocyanate was condensed with (XXXIX) and (XL), severally, and the resultant

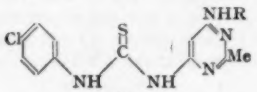

(XXXVII.)

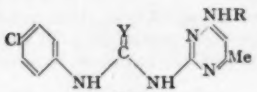

(XXXVIII.)


(XXXIX.)


(XL.)

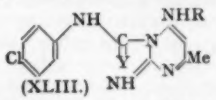
thioureas were converted into the guanidines by reaction with ammonia. In contrast to the corresponding arylaminopyrimidines, *both* of the new isomers provided active substances, and indeed, one compound of type (XXXVIII), which by analogy with (XXVI) should be quite inactive, was almost as effective as the best substance of type (XXXIII).

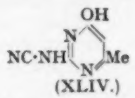

(XLI.)

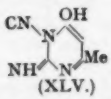

(XLII.)

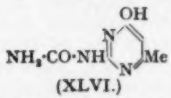
The thiourea (XLI; Y = S),[21] an intermediate in the preparation of (XXXVIII), together with (XLII; Y = S) [22] which resulted from the reaction of *p*-chlorophenyl *iso*thiocyanate with (VII), were themselves examined biologically and found to be entirely devoid of antimalarial effect. Likewise, the normal urea (XLII; Y = O) [22] from *p*-chlorophenyl *iso*cyanate and (VII) was inactive.

In the course of the investigation of these reactions, it was possible to settle constitutional doubts which existed regarding the precise structures of (XXXI), and hence of (XXXIII), and (XLII; Y = S or O). The several synthetic routes described above might equally have yielded isomeric substances such as (XLIII; Y = NH, S, or O). It was discovered, however, that the 2-methylthiopyrimidine (XXX*a*) when heated with *p*-chlorophenylguanidine [21] gave a product identical with (XXXI; X = Cl) which along with the derivative (XXXIII) must


(XLIII.)

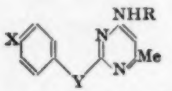

(XLIV.)

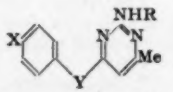

(XLV.)


(XLVI.)

therefore have the orientation indicated; (XXXI; X = Cl) was also obtainable from *p*-chloroaniline and (XLIV), the reaction product from dicyandiamide and ethyl acetoacetate, which cannot then have the alternative structure (XLV); (XLIV) on hydrolysis gives (XLVI), and when this is heated with *p*-chloroaniline and its OH group is converted into NHR, it yields, and establishes the constitution of (XLII; Y = O). Finally, since (XXXIII; X = Cl) resulted from the reaction of ammonia and mercuric oxide with (XLI), the latter had the structure shown.

(XLVII.)



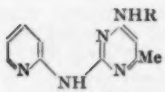

(XLVIII.)

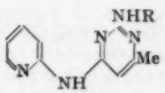
The investigation of the ether and thioether analogues of (XVI) and (XXIV) was called for,[23] if only because of the formal resemblance that these compounds (XLVII; Y = O or S) and (XLVIII; Y = O or S) still retained to riboflavin. Access to these substances was

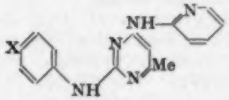
through condensation of the appropriate 2(or 4)-chloro-4(or 2)-basic side chain pyrimidine with a nuclear-substituted phenol or thiophenol. Of the 20 substances prepared, antimalarial activity was detected only in type (XLVIII; X = MeO, Y = O or S), with the thio-compounds markedly more effective than the oxygen ether type. Indeed, (XLVIII; X = MeO, Y = O, R = $CH_2 \cdot CH_2 \cdot NEt_2$) was almost as active as (III). The *p*-chlorophenyl ethers were entirely devoid of therapeutic action.

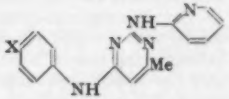
(c) *Various heterocyclic systems linked to pyrimidine.* Up to this stage of the research it seemed that the most useful therapeutic agents resulted from the association of pyrimidine with a benzenoid system. A further variation was now made in which the latter was replaced by a second heterocyclic structure, notably pyridine, quinoline, pyrimidine, or benziminazole.

(i) Pyridylaminopyrimidines.[24] The first compounds made were (XLIX) and (L), analogous to (III) and (XXIV), respectively, and prepared by similar methods. In addition, because


(XLIX.)

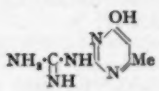

(L.)

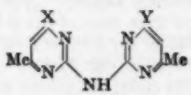

(LI.)

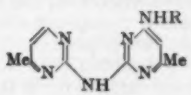

(LII.)

of the intrinsic basic properties of aminopyridine, it was thought that this residue might replace the basic side chain in the arylaminopyrimidine class. Compounds type (LI) and the isomeric (LII) were accordingly made. Not one of the several preparations, however, showed positive activity.

(ii) Dipyrimidylamines.[24] After a few abortive attempts to prepare substances of this class by causing chloropyrimidines to react with aminopyrimidines, a method involving total synthesis of the second pyrimidine ring was selected. Thus (LIII), from (XLIV) and ammonia,


(LIII.)

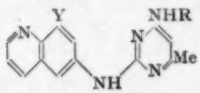

(LIV.)

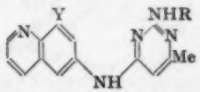

(LV.)

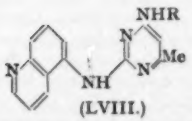
or diguanide and ethyl acetoacetate, condensed either with acetylacetone or more ethyl acetoacetate to give (LIV; X = Me, Y = OH, or X = Y = OH). Conversion of hydroxyl into chloro-, followed by reaction with alkylamines, gave, *e.g.*, (LV) and the related (LIV; X = Y = NMe_2 and $NHPr^i$). Here again, not one single substance exhibited antimalarial activity.

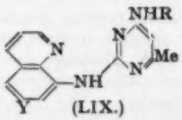
(iii) Quinolylaminopyrimidines.[25] Two possibilities were evident in this class, since the amino-linkage to the quinoline could be in either the heterocyclic or the benzene ring. The

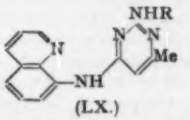
(LVI.)




(LVII.)


(LVIII.)

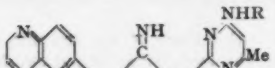

(LIX.)

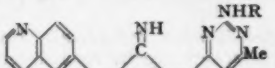

(LX.)

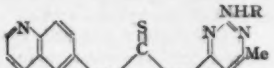
former were, of course, related to pyridylaminopyrimidines (XLIX), while the latter could be regarded as di-*o*-substituted arylaminopyrimidines. Examples of the latter only were made [25] (LVI—LX; Y = H or OMe), essentially the same synthetic route being utilised as that in which (XXX*a*) was the starting material, the linkage to the quinoline residue being at positions 5, 6, and 8. Of these preparations, only those based on (LVI; Y = H) were active. The corresponding (LVI; Y = OMe) was, surprisingly, quite inactive, as was also (LIX; Y = OMe) which was closely related to pamaquin (I).

[24] Curd, Graham, and Rose, *J.*, 1948, 594.
[25] Curd, Graham, Richardson, and Rose, *J.*, 1947, 1613.

At this point, it is convenient to include the quinolylguanidinopyrimidines [26] of which two types were made, (LXI) and (LXII), corresponding to the highly active (XXXIII) and (XXXVII) in the phenylguanidinopyrimidine series. The preparative methods were analogous to those used for the latter, namely, beginning with the condensation of 6-diguanidoquinoline and ethyl

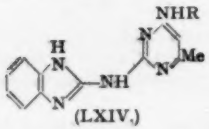

(LXI.)

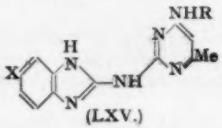

(LXII.)

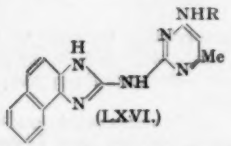

(LXIII.)

acetoacetate for (LXI), and amidation of the thiourea (LXIII), obtained by the interaction of 6-*iso*thiocyanatoquinoline and (XXXIX), for (LXII); (LXI) alone exhibited antimalarial activity, and that but slight at high dosage.

(iv) Benziminazolylaminopyrimidines.[27] Only derivatives of 2-aminobenziminazole were made, which could therefore be regarded as derived from (XXXIII). The 15 preparations included the parent benziminazole (LXIV), those with substituents at position 5 (=6) (LXV), and the naphthiminazole (LXVI). The simplest synthesis of these compounds involved the


(LXIV.)

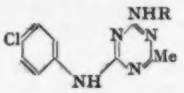

(LXV.)

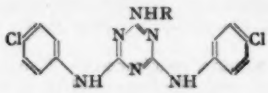

(LXVI.)

initial condensation of the appropriate *o*-phenylenediamine with (XLIV), followed by halogenation and reaction with the basic side-chain amine. Type (LXVI) was inactive, but (LXIV) had a marked therapeutic effect, greater than that of the related (XXXIII; X = H). Methyl and chloro-substituents (LXV; X = Me or Cl) both activated, but methoxyl deactivated.

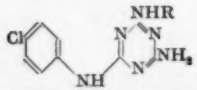
1 : 3 : 5-*Triazines*.[28]—The investigation of derivatives of 1 : 3 : 5-triazines was made after the discovery of activity in the diguanide class, but many of the compounds prepared so closely resemble the early arylaminopyrimidines that they are more conveniently described at this point. Two synthetic routes were used: the first, based on ring closure of diguanides with acetic anhydride, gave guanamine derivatives (LXVII), while the second was based on step-

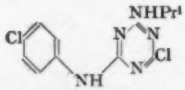
(LXVII.)




(LXVIII.)

(LXIX.)



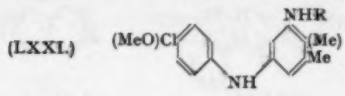

(LXX.)

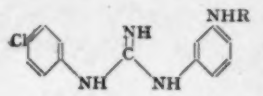
wise replacement of the three chlorine atoms of cyanuric chloride. In the latter type, one chlorine atom was replaced by the aniline residue (*p*-chloroaniline or *p*-anisidine), the second by another amine residue which was either a further aniline or an alkylamine, sometimes of the basic side-chain class, while the third chlorine, now much less reactive, was either left intact, or by heating the compound with the appropriate substance converted into hydroxy-, amino-, ethoxy-, or dialkylaminoalkylamino-. The compounds (LXVIII—LXX) were typical of the 20 or more of the members of this class that were made, not one of which, together with (LXVII), the exact analogue of (III), showed even the slightest trace of antimalarial activity.

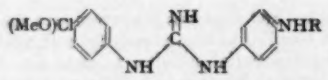
Diphenylamines and Diphenylguanidines.[29, 30]—The discovery of therapeutic activity in the arylamino- (XVI) and arylguanidino-pyrimidines (XXXII) seemingly lent support to the working hypothesis by means of which they had been evolved, while the experimental demon-

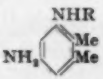
[26] Gulland and Macey, *J.*, 1949, 1257.
[27] Basford, Curd, and Rose, unpublished work.
[28] Curd, Landquist, and Rose, *J.*, 1947, 154.
[29] Mann and Porter, *J.*, 1947, 910.
[30] Mann, Naylor, and Porter, *J.*, 1947, 914.

stration of anti-vitamin properties with respect to riboflavin and the growth of *Lactobacillus casei* suggested a mechanism for their plasmodicidal action. The two relevant factors, one associated with potential tautomerism, and the other a general structural resemblance to the growth factor might, or might not, have been related. An investigation was put in hand by


(LXXI.)


(LXXII.)

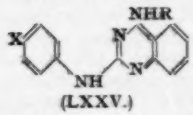

(LXXIII.)

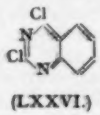

(LXXIV.)

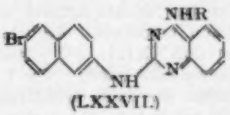
Mann and his co-workers which sought to throw some light on these matters by preparation of the compounds (LXXI) [29] and (LXXII) [30] formally analogous with (XVI) and (XXXIII), but having the pyrimidine nucleus replaced by benzene so that the tautomeric features characteristic of the former were abolished or at least greatly diminished. In addition, the *p*-isomer (LXXIII) of (LXXII) was made as a variant, and also the diaminoxylene (LXXIV) because of its formal resemblance to the active pyrimidine derivative (X). (LXXII) and (LXXIII) resulted from the condensation of the *p*-methoxy- or *p*-chloro-phenylcyanamide with the appropriate phenylenediamine. (LXXI) and (LXXIV) were prepared by standard procedures, except that the basic side chain was introduced by the device of reducing an anil group formed from primary amino- and 5-diethylamino-*n*-pentan-2-one diethyl ketal.

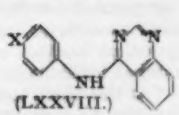
With regard to antimalarial activity, all the diphenylamines (LXXI), the simpler xylenes (LXXIV), and the diphenylguanidine (LXXIII) were entirely without action. On the other hand, (LXXII) showed quite marked activity, less than that of the pyrimidine analogue (XXXIII), but of the same order as (III).

Quinazolines.[32–35]—Since the association of a pyrimidine nucleus with a substituted benzene ring had been found to provide a basis for antimalarial activity, it was clearly of interest to examine derivatives of quinazoline in which these two cyclic systems were fused together. Additional support for this investigation also arose from the structural relationship between quinazoline and quinoline. Earlier work by Magidson and Golovchinskaya [31] had failed to disclose therapeutic effect in simple quinazolines carrying alkylaminoalkyl groups, but their preparations had not included arylamino-substituents. The latter were now introduced at position 2, yielding substances (LXXV) [33] analogous to the earliest arylaminopyrimidines (XVI), or more precisely the corresponding 5 : 6-disubstituted pyrimidines. The preparation


(LXXV.)


(LXXVI.)


(LXXVII.)


(LXXVIII.)

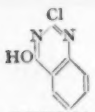
of these compounds was facilitated by the ease with which the basic side-chain amine could be made to react almost quantitatively with the 4-chloro-substituent of (LXXVI). A large series was made and activity was found in almost every member. A *p*-chloro-substituent again gave optimal effect, fully equal to that of type (XXXIII), but (LXXV; X = H, Me, MeO, MeS, and NO_2) were also quite highly active. In contrast to the arylaminopyrimidine series, the bromonaphthylamino-group in (LXXVII) was dystherapeutic.

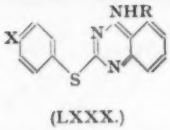
The influence of substitution in the benzene ring of the quinazoline system (LXXV; X = Cl) was examined.[34] Substituents such as chloro-, nitro-, amino-, methyl, methoxyl, and benzo- were variously introduced into positions 5, 6, 7, and 8. Activity was retained in every instance, but always less than that of the parent compound.

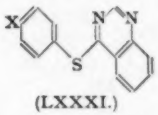
The isomeric type (LXXVIII) analogous to the active arylaminopyrimidines (XXIV) was also studied.[35] The preparative route from (LXXVI) and arylamines was first investigated,

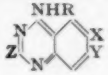
[31] Magidson and Golovchinskaya, *J. Gen. Chem. Russia*, 1938, **8**, 1797.
[32] Curd, Landquist, and Rose, *J.*, 1947, 775.
[33] Chapman, Gibson, and Mann, *J.*, 1947, 890.
[34] Curd, Landquist, and Rose, *J.*, 1948, 1759.
[35] Curd, Hoggarth, Landquist, and Rose, *J.*, 1948, 1766.

but although essentially pure 2-arylamino-4-chloroquinazolines were produced, these on further reaction with basic side-chain amines gave the 4 : 6-bisdialkylaminoalkylaminoquinazolines as the main products. A route starting with (LXXIX) [from hydrolysis of (LXXVI)],


(LXXIX.)


(LXXX.)

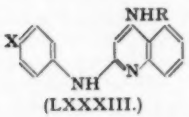

(LXXXI.)

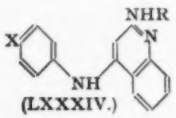

(LXXXII.)

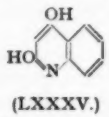
which reacted with basic side-chain amines, and then was converted into the 4-chloro-derivative, proved satisfactory, and in this way a number of compounds type (LXXVIII) was prepared, all of which, however, were devoid of antimalarial activity, as were also the related arylthioquinazolines (LXXX) and (LXXXI) [compare inactive (XLVII) and active (XLVII; Y = S)].

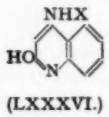
Finally, in the quinazoline series, the observation was made that the simple 4-basic side-chain derivatives were themselves active [33] (at variance with the findings of Magidson and Golovchinskaya [31] whose negative results were probably due to the insusceptibility of their test-strain), and this called for a systematic study of type (LXXXII; Z = H, X and/or Y = Cl, MeO, NO_2). Nearly 50 variants were made, nearly all of which were active. A 7-chloro-substituent provided highest activity, again of the same order as that of (XXXIII; X = Cl). Compound (LXXXII; Z = NH_2, X = Y = H) which was related to the active 5 : 6-dimethylpyrimidine (X), also showed considerable therapeutic effect.

Arylaminoquinolines.[36, 38]—Although, as recorded above, the quinoline nucleus had already been the subject of extensive chemotherapeutic researches, no derivatives had been prepared carrying arylamino-substituents analogous to the pyrimidines (XVI) and (XXIV). Compounds of type (LXXXIII) and (LXXXIV) were therefore prepared initially,[36] the starting material in both instances being 2 : 4-dihydroxyquinoline (LXXXV) which, when heated


(LXXXIII.)

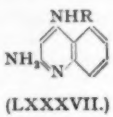

(LXXXIV.)

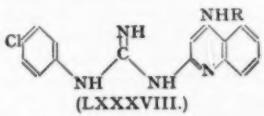

(LXXXV.)

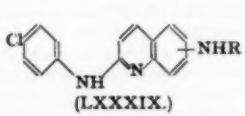

(LXXXVI.)

with excess of arylamine (in the presence of a salt such as hydrochloride), or excess of basic side-chain amine, gave the intermediate (LXXXVI; X = aryl or dialkylaminoalkyl). The latter, by the usual procedure, then led to (LXXXIV) and (LXXXIII), respectively. Of these two types, (LXXXIII) was much the more active, being comparable with the corresponding pyrimidines (XVI), and the highest activity was achieved, as before, with *p*-substituents such as chlorine, nitro-, and methoxyl. Additional substituents were introduced into the quinoline nucleus of type (LXXXIII), for example, 3-methyl and 7-chloro-, but without marked influence on the therapeutic effect. The 7 : 8-benzo-derivative was, however, inactive.

At this point, some attempt was made to determine whether the activity of these compounds was due to their structural relation to the earlier pyrimidines, or whether they were simply to be regarded as derivatives of 4-dialkylaminoquinolines which at that time had just become


(LXXXVII.)


(LXXXVIII.)

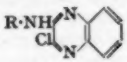

(LXXXIX.)

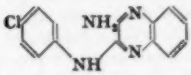
known as antimalarial agents.[37] Although closely allied compounds of type (LXXXVII) were made and found to be highly active, while the related (LXXXVIII), prepared from the latter *via* the intermediate thiourea (compare XLI), was completely inactive, no definite conclusions could be drawn. An additional aspect was provided by the preparation of isomers of (LXXXIII), but with the basic side chain in the benzene ring of the quinoline at positions 5, 6, and 8, respectively (LXXXIX).[38] These compounds were inactive.

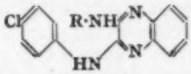
[36] Curd, Raison, and Rose, *J.*, 1947, 899.
[37] Schönhöfer, *Z. physiol. Chem.*, 1942, **274**, 1.
[38] Bennett, Crofts, and Hey, *J.*, 1949, 227.

Quinoxalines.[39-41]—Apart from the obvious relation of quinoxaline to quinoline, its recognition as part of the riboflavin molecule provided an additional reason for the examination of this system as the basis for potential antimalarial agents. Syntheses in this series (45 compounds) were based initially on 2 : 3-dichloroquinoxaline (XC).[39] Stepwise replacement of

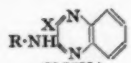
(XC.)

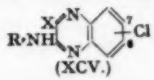

(XCI.)

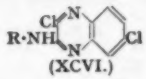

(XCII.)


(XCIII.)

the chlorine atoms by amine residues gave compounds such as (XCI) (active), (XCII) (inactive), and (XCIII) (inactive). The importance of the chlorine substituent in (XCI) was demonstrated by the inactivity of (XCIV; X = H, Me, OH, or NH_2) obtained from the appropriate monochloroquinoxalines.[40] Substituents (Cl, Br, Me, OMe, NO_2) were introduced into the benzene


(XCIV.)

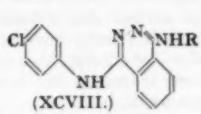

(XCV.)


(XCVI.)

ring of the quinoxaline system.[41] These substituents in position 6 (some in 7), giving, *e.g.*, (XCV; X = NHPh, OH, S, OEt, or H), had no marked effect on the therapeutic properties of the parent structures, whether initially active or inactive. An exception was chlorine in position 6, which produced derivatives, notably type (XCVI), that were more active even than mepacrine (II) and (XXXIII).

Cinnolines[42] (*Phthalazines and* iso*Quinolines*).[39]—During the course of earlier work with cinnoline, Simpson and his co-workers had appreciated the potentialities of this nucleus for the production of chemotherapeutic agents. This section records those substances, of which some 20 examples were made, specifically designed as antimalarials.[42] They were all derivatives of 4-aminocinnoline (XCVII) with substituents (Cl, Me, OMe) in positions 6 and/or 7 and prepared by reaction of the appropriate amine with the 4-phenoxycinnoline. The parent

(XCVII.)


(XCVIII.)

(XCIX.)

compounds (XCVII; X = Y = H) showed feeble activity which was markedly strengthened, in particular, by the introduction of chlorine at position 7 (compare quinoxalines). A second chlorine at 6, giving (XCVII; X = Y = Cl), slightly reduced this activity. Therapeutic effect fell off rapidly with the heavier basic side-chains.

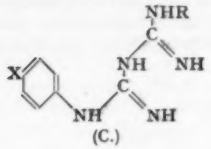
The preparation of single examples based on phthalazine (XCVIII) and *iso*quinoline (XCIX) may be mentioned here[39]—the former was weakly active at high doses, the latter quite inactive.

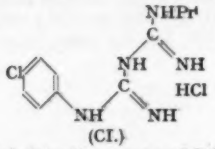
Diguanides.[43-50]—The sequence in which the foregoing chemical types have been recorded has been based largely on convenience of cross-reference, and only initially on approximate chronological order, so that, although it is most convenient to have left the diguanides until now, the first members of this series were actually synthesised within a year of the discovery by Dr. D. G. Davey of activity in the pyrimidines (XVI) against his experimental infections. By that time, exploitation of the lead presented by the latter compounds had produced so

[39] Haworth and Robinson, *J.*, 1948, 777.
[40] Crowther, Curd, Davey, and Stacey, *J.*, 1949, 1260.
[41] Curd, Davey, and Stacey, *J.*, 1949, 1271.
[42] Keneford and Simpson, *J.*, 1947, 917.
[43] Curd and Rose, *J.*, 1946, 729.
[44] Curd, Hendry, Kenny, Murray, and Rose, *J.*, 1948, 1630.
[45] Crowther, Curd, Richardson, and Rose, *J.*, 1948, 1636.
[46] Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1645.
[47] Ainley, Curd, and Rose, *J.*, 1949, 98.
[48] Ashworth, Crowther, Curd, Hendry, Richardson, and Rose, *J.*, 1949, 475.
[49] Crowther, Curd, and Rose, *J.*, 1951, 1780.
[50] Crowther, Curd, Davey, Hendry, Hepworth, and Rose, *J.*, 1951, 1774.

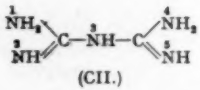
many new highly active types that the emergence of yet another in the form of the diguanides created no novel situation, and it was not possible to appreciate at that stage its ultimate importance.

The selection of this particular system for study was based on earlier chemical experience gained from its incorporation in speculative drug molecules of the sulphanilamide class, and on the realisation that it provided an acyclic structure bearing a close formal resemblance to the early anilinopyrimidines (XVI), while retaining some of the features of potential tautomerism which at that time were considered necessary for therapeutic effect. The structure (C; X = Cl), carrying a basic side-chain radicle, was the first prepared.[43] It is here formulated in the manner in which a model of the molecule appears in the planar form, and which best shows its shape relationship to type (XVI). Surprisingly, it was entirely devoid of antimalarial activity.


(C.)

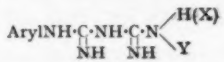

(CI.)

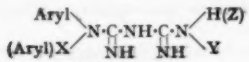
(" Paludrine "; proguanil B.P.C.)

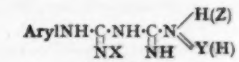

(CII.)

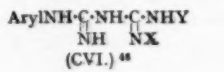
Fortunately, experience of inactivity in earlier molecular types carrying two basic side chains immediately led to the suggestion that the dialkylaminoalkyl group of (C) was superfluous in association with the equally highly basic diguanide system. Its replacement, in the first instance by diethyl and piperidyl, led to the immediate re-emergence of antimalarial activity. Routine variation led in due course to " Paludrine " (= proguanil B.P.C.) (CI).[43] In addition to the normal therapeutic type of activity, compounds of the diguanide class were found by Dr. Davey to exhibit causal prophylactic action, in that they appeared to attack the parasite in the earlier pre- or exo-erythrocytic phase of its life cycle, and it was undoubtedly this unique observation that provided the stimulus for the very considerable effort then directed towards the type. In all, some 200 diguanides have been prepared and examined, together with probably an equal number of miscellaneous compounds whose molecules simulate in part, or in their entirety, the disposition of carbon and nitrogen atoms peculiar to the diguanide structure. A detailed record of these is clearly impossible here, and is indeed unnecessary since it is hoped shortly to publish elsewhere a full discussion of all the compounds made under this heading. Instead, it is proposed to record the main lines of investigation with some indication of the relative therapeutic effects.

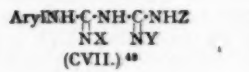
To assist appreciation of the structural chemical features, it is first necessary to point out the essential symmetry of the diguanide molecule (CII) and the actual equivalence of the nitrogen atoms N^1, N^3, N^4, and N^5, so that the conventional arrangement of the double bonds, and therefore of the hydrogen atoms, at any rate in diguanide itself, has no real significance. Substitution of hydrogen atoms by aryl and alkyl residues, especially poly-substitution, would

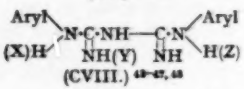

(CIII.) [43–46]

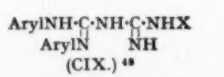

(CIV.) [45, 46, 47]

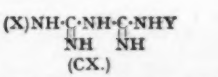

(CV.) [45, 47, 48]

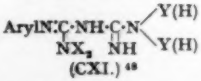

(CVI.) [48]


(CVII.) [48]


(CVIII.) [45–47, 48]

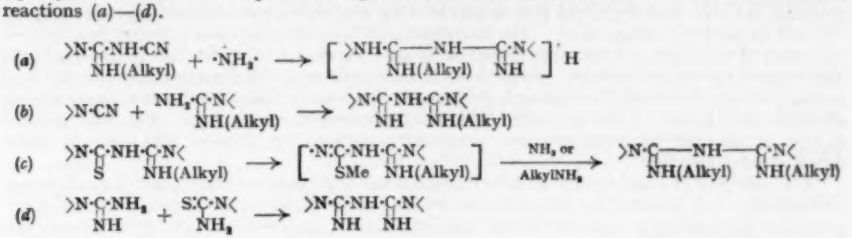

(CIX.) [48]


(CX.)

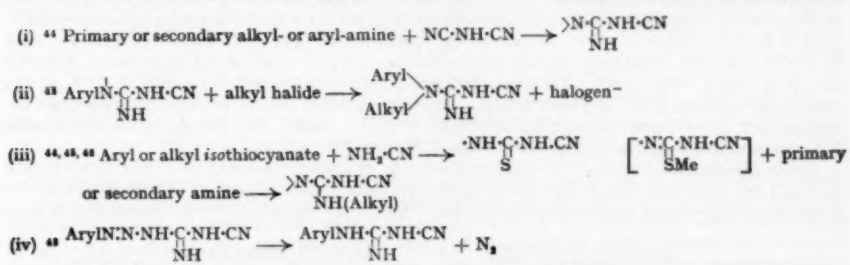

(CXI.) [48]

in certain instances fix the position of double bonds, but this aspect requires fuller discussion than is now convenient. Since all seven hydrogen atoms were potentially replaceable, a great number of variations was possible. Naturally, not all were made, but sufficient were investigated to enable working rules to be formulated. Some 14 main types were prepared, represented by the alternatives provided in (CIII—CX; X, Y, and Z = alkyl), together with many other individual variations, such as that seen in (CXI). The preparative routes were, in detail,

equally numerous, but it is possible to generalise. Most were based on the four fundamental reactions (*a*)—(*d*).



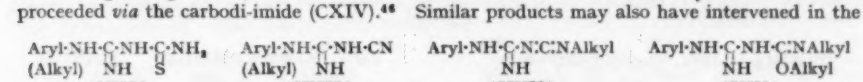
The dicyandiamide derivatives used in route (*a*) were themselves prepared by several reactions, *viz.*, (i)—(iv), and the guanylthioureas of route (*c*) resulted from interaction of



aryl or alkyl *iso*thiocyanates with guanidines, followed by methylation to give, where required, the guanyl *S*-methyl*iso*thioureas.[45]

The reaction of the dicyandiamides with amines (route *a*) was effected at temperatures between 50° and 150° with the amines present either as a salt,[44, 45, 46] or alternatively as the base in the presence of a copper salt,[43] in which case the diguanide was isolated as its copper complex. For route (*b*), the mono- or di-alkyl- or -aryl-cyanamides were brought into reaction with the mono- or di-substituted aryl- or alkyl-guanidines in boiling solvents such as butanol.[47]

Route (*c*) [45, 46, 48] was thought in some respects to follow a complex course. When the *N*-aryl- or *N*-alkyl-guanylthioureas (CXII) were converted into their *S*-alkyl *iso*-derivatives, reaction of these with amines yielded diguanides without the intervention of a desulphurising agent. When, however, they were treated with amines direct, a desulphurising agent such as mercuric oxide was required and the dicyandiamide (CXIII) was the main product, some of which then passed into the diguanide. Similar treatment of the *N*-arylguanyl-*N'*-alkylthioureas gave diguanides, but for a number of reasons it was considered likely that the reaction proceeded *via* the carbodi-imide (CXIV).[46] Similar products may also have intervened in the



conversion of the above-mentioned *S*-alkyl-*N'*-alkyl-*N*-arylguanyl*iso*thioureas into guanidines, since in the presence of alcoholic solvents good yields of *O*-alkylureas (CXV) were frequently obtained.

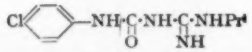
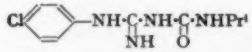
With regard to antimalarial activity, although so many different variants were examined, the results were capable of fairly simple analysis. The first important point was the parallelism between therapeutic and prophylactic effect which was complete throughout. The second was the unique position of the *iso*propyl group, since whatever variations were made elsewhere in the molecule, with regard to substitution either in the benzene ring or in the diguanide chain itself, this member of the homologous alkyl series, when present in a terminal nitrogen, always provided maximum activity, where activity was at all apparent. *n*-Propyl compounds were nearly as effective, but activity fell away rapidly on either side, the methyl homologues being inactive. The third important point was the need for one aryl group in the drug molecule on the nitrogen atom remote from that carrying the *iso*propyl group. More than one aryl residue

always deactivated completely. In brief then, the essential structural basis for high antimalarial activity was the diguanide molecule with a phenyl or substituted-phenyl group at N^1, and an *iso*propyl group at N^5. The introduction of a second alkyl group always deactivated, the order of diminishing therapeutic effect being with alkyl at N^5, N^2, N^4, and N^1, successively. The importance of the *iso*propyl group at N^5 in this series was well illustrated by the still high activity of the N^2-ethyl-N^5-*iso*propyl compounds (aryl = *p*-chlorophenyl) and the complete absence of activity in the isomeric N^5-ethyl-N^2-*iso*propyl compounds. (CI) with methyl groups at N^3 and N^4 retained slight antimalarial action, but heavier alkyl groups again deactivated completely.

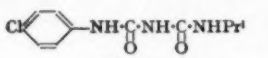
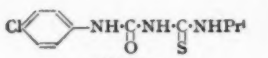
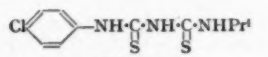
The influence of a wide range of substituents in the aryl (nearly always phenyl) nucleus was investigated. In general, the picture was similar to that seen in the arylamino- and arylguanidino-pyrimidine prototypes (XVI) and (XXXIII), respectively, but there were a few notable exceptions; for instance, while nitro-, methyl, and methylthio-substituents provided activity, cyano- did not. Moreover, the bromo- and iodo-analogues were at least as effective as the chloro-compounds.[49, 50] The mass of these heavier halogen substituents could be distributed in the form of two chlorine atoms at positions 3 and 4, giving a substance (CIII; Aryl = 3 : 4-$C_6H_3Cl_2$, Y = Pr^i) considerably more active, but also much more toxic, than (CI).[49, 50] Of the remaining dichloro-possibilities, only 3 : 5-disubstitution gave activity, but at a much lower level. The introduction of any substituent into one or both of the *o*-positions destroyed activity absolutely. Another contrast to the pyrimidine series was the inactivity of the 6-bromo-2-naphthyl analogue of (CI). Lastly, the N^1 : N^5-dialkyldiguanides (CX), even di*iso*propyldiguanide, were without antimalarial action.

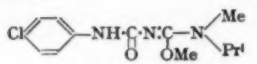
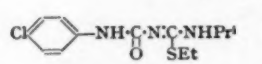
Guanylureas and Biurets.[51, 52]—The preparation of guanylthioureas of types (CXVI) and (CXVII), for example, and of the derived guanyl-*S*-alkyl*iso*thioureas, as intermediates in the synthesis of diguanides was mentioned above. They were examined for plasmodicidal action,

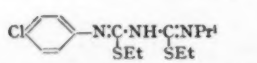
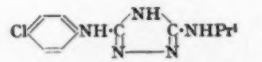
(CXVI.) Aryl·NH·C(=S)·NH·C(=NH)·NHPr^i Aryl·NH·C(=NH)·NH·C(=S)·NHPr^i (CXVII.)

(CXVIII.)  (CXIX.) 

with negative results. The guanylurea (CXVIII) analogous to (CXVI) was, however, quite highly active, but in the therapeutic assay only. The high activity of the homologous *N*-methyl derivative provided a further contrast to the related diguanide series. (CXVIII) resulted by direct synthesis from *p*-chlorophenyl *iso*cyanate and *iso*propylguanidine and indirectly from hydrolysis with cold dilute mineral acid of, or the action of nitrous acid on, the corresponding diguanide (CI; proguanil).[51, 53] The isomeric *N*-chlorophenylguanyl-N^1-*iso*propylurea (CXIX) was inactive.

 (CXX.)  (CXXI.)  (CXXII.)

(CXXIII.)   (CXXIV.)

(CXXV.)   (CXXVI.)

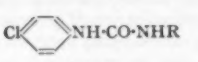
A series of related biurets,[51] monothiobiurets, and dithiobiurets [52] was also prepared and examined. These included (CXX), (CXXI), and (CXXII) which bore an obvious relationship to (CI), and also a number of *iso*-analogues, for example, (CXXIII), (CXXIV), and (CXXV). The latter were, for the most part, intermediate substances resulting from the action of *iso*cyanates and *iso*thiocyanates on ureas and *iso*ureas which were then hydrolysed or sulphurised to the corresponding normal biurets. (CXXV), obtained by further ethylation of the corresponding 1-*p*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret (from *iso*propyl *iso*thiocyanate and *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea) was of particular importance since with hydrazine

[51] Curd, Davey, and Richardson, *J.*, 1949, 1732.
[53] Curd, Davey, Richardson, and Ashworth, *J.*, 1949, 1739.

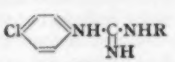
it gave the 1 : 2 : 4-triazole (CXXVI) [53] so closely related to (CI), but which, like all the other substances just described, was completely devoid of antimalarial activity.

Miscellaneous.—Many hundreds of compounds fall under this heading, resulting for the most part from single speculative variations on the main themes, and it is not possible to record them all here. There are a number of groups and individuals, however, the results from which provide some interest in relation to the main developments, and a selection is given below.

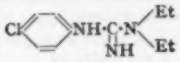
In most of the types discussed in the foregoing sections, the central nucleus could be regarded as providing a chemical link between an aromatic system and an alkylamino-group. At a comparatively early stage the possibility that therapeutic effect might result from a much less complex type of linkage was examined, and simple ureas and guanidines were made. These included compounds of type (CXXVII) (compare the active CXVIII), (CXXVIII), (CXXIX), CXXX), and (CXXXI). Of these, only (CXXVIII) showed activity, and that marginal.



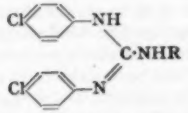
(CXXVII.)



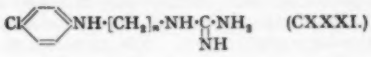
(CXXVIII.)



(CXXIX.)

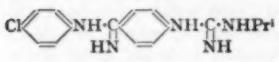


(CXXX.)

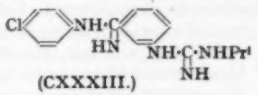


(CXXXI.)

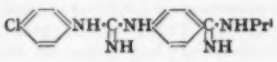
A further variation of the diguanide type was provided by a number of structures in which the diguanide chain was interrupted by a benzene ring, giving, *e.g.*, (CXXXII), (CXXXIII), and (CXXXIV), and the related simpler unalkylated types (CXXXV), (CXXXVI), and (CXXXVII). These substances were all derivatives either of diphenylamidine or diphenylguanidine [compare types (LXXI) and (LXXII)]. The former were made from the corresponding nitrobenzchloroanilides *via* the imino-chlorides and nitroamidines, and the latter from the diphenylguanidine-*p*-imino-ethers. (CXXXV) was slightly active, the remainder inactive.



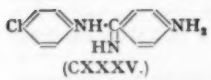
(CXXXII.)



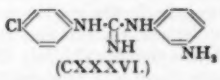
(CXXXIII.)



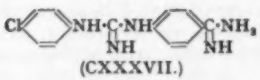
(CXXXIV.)



(CXXXV.)



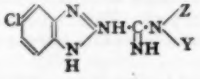
(CXXXVI.)

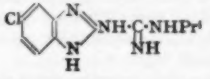


(CXXXVII.)

Benziminazolylaminopyrimidines (LXV), analogous to the original arylaminopyrimidines, have already been mentioned. Several benziminazoles similarly analogous to the diguanide agents were prepared, mainly by reaction of the appropriate alkyldicyandiamide with an *o*-phenylenediamine. Chief interest attaches to the series (CXXXVIII) and (CXXXIX). The

(CXXXVIII.)





(CXXXIX.)

latter, *i.e.*, the exact analogue of (CI; proguanil), was entirely devoid of activity. The former, especially (CXXXVIII; Z = Y = Me), was quite active at high and toxic doses.

Discussion.

The beneficial effect of a chemotherapeutic agent may arise either from an indirect action involving stimulation of the host in some manner, or more commonly from a direct action on the pathogen. In the latter event, two factors have to be considered, access and intrinsic activity. The first is compounded of a number of variables such as solubility, absorption from the host alimentary tract or site of injection, rate and mode of excretion, metabolism, and so on, while the second, although at first glance simpler, might involve permeability considerations with respect to the cell, if there be such, of the disease incitant, diffusion to the ultimate site of action, and also consideration of the ability of the cell to detoxify or rid itself

of the foreign chemical substance. In a disease such as malaria, the situation is complicated by the existence of a life cycle for the causative parasite so that therapeutic effect might result from drug action at one or more different phases, some of which are intracellular in habitat.

The existence of this large number of variables, and many more, is frequently overlooked by those who would too easily rationalise the course of chemotherapeutic research, but equally it confounds those who attempt to explain observed facts in terms of simple and often entirely artificial systems. That is why the use of the " working hypothesis " concept based on observation and the intelligent development of leads, related where possible to a theoretical mode of action, must constitute the foundation for speculative research in this field for a long time to come.

For the same reasons, the mass of chemical and biological data that has arisen from the research under consideration is still insufficient for a critical analysis to be made, since modifications in chemical structure that bring about parallel changes in the overall chemotherapeutic effect of several drug types may do so by influencing different and separate pharmacological characteristics. For example, the basic alkyl side chain that appears in many active compounds may have a diversity of functions. It is known, for example, that its presence in a molecule leads to concentration in the erythrocytes and many other solid tissues of the animal body, clearly a desirable effect when dealing with an infection that is predominantly intracellular, but unpublished work, carried out in these laboratories by Dr. Madinaveitia on bacterial growth, would also suggest that the basic side chain exhibits specificity with regard to intrinsic antimicro-organismal action. For convenience, details of the basic side-chain groups in respect to the different drug types were not given in the preceding sections, but it was notable that in some instances optimum activity was provided by the lighter groups, *e.g.*, 2-dimethylaminoethylamino-, while in others the heavier (longer) and more complex groups were required (as in I). In still others, maximum activity resulted from the use of side chains of intermediate size. This would accord with the concept of multiplicity of function for the side chain, conditioned by the different physical and chemical properties inherent in the remainder of the drug molecule.

Study of many of the active types reveals, however, that strong basic properties can be provided by groups other than di- and tri-alkylamine systems. Thus, the phenylguanidinopyrimidine (XXXVI) was highly active, in contrast to the related inactive and much less basic (XVII). This result suggested that the phenylguanidine residue was operative. Physicochemical studies supported this view. For example, the dissociation constant of *p*-chlorophenylguanidine itself was found to be 10·6, while that for *p*-chloroaniline, the corresponding unit in (XVII), was 4·7.[53] The dissociation constant associated with the terminal nitrogen atom of typical basic side-chain amines was in the region 9·5—10·5.[51] On this basis, it is perhaps not surprising that the diphenylguanidine analogue (LXXII) of (XXXVI) exhibited some antimalarial activity, while the diphenylamine (LXXI) did not.

In the diguanide series, the diguanide chain was presumed to provide the necessary basic function. Thus, the higher of the two dissociation constants of *p*-chlorophenyldiguanide was found to be 10·4.[53] This was not varied more than a single unit by mono- or poly-alkylation of the nitrogen atoms, so that the various activations and deactivations produced by such modification could not be explained on this basis.

The presence of two basic groups each with a pK value around 10 in the same molecule always deactivated in the numerous drug types examined. These could be two alkylamine systems, or two diguanide structures (of which several were made, but no examples are given above), or one of each type.

The need for one group in the molecule giving a high overall cationic charge thus seemed clear, but a more subtle requirement appeared in relation to a second basic function. The early working hypothesis on which these researches were launched took note of the presence within active molecules of potential tautomerism. Although initially concerned with a guanidine type of structure (acyclic or cyclic), further study showed that it could be associated with the simpler amidine configuration occurring either as such, or as a vinylogue, for example, in the 4-aminoquinolines and (II). As a consequence, it became much more attractive to abandon the principle of tautomerism, which in any event never had any foundation in fact, and reconsider the problem in the light of the properties of amidine groups, conditioned as they were by considerations of resonance energies. It then appeared that in all active molecules of the types being discussed an amidine group or a vinylogous structure was essential, associated

[53] Gage, *J.*, 1949, 221.

either with an aromatic or an alkyl group, or both, and so influenced by relevant substituents that at physiological hydrogen-ion concentrations it was present largely as the amidinium ion. This was an empirical observation that at the moment seemed quite incapable of explanation, but which accounted for a number of apparently anomalous therapeutic results.

For example, the second pK constants associated with the active arylaminopyrimidines (XVI) and (XXV), which must be due to the heterocyclic system, were both around 6·6, while those of the analogous, but inactive arylaminopyrimidine (XXVI) and arylaminotriazine (LXVII) were 5·5 and 4·05, respectively.[53] The active 4-aminoquinazolines of type (LXXXII; Z = H) had a value of about 7·6.[54]

The diguanides apparently constituted a special case.[53, 54] These structures had a second dissociation constant, but too low (about 2) to have any biochemical significance. Instead, it must be assumed that the first dissociation constant not only provided the function normally associated in other types with the basic side chain, but also fulfilled the second criterion for activity in that it was of sufficient magnitude and arose from the amidino- or hetero-portions of the molecule, which must then be in the requisite protonised form under physiological conditions.

In considering antimalarial drugs as a whole, there are some notable omissions from the scheme, for example, quinine, the quinoline-carbinols, and pamaquin (I), except that all of these carry a side-chain alkylamine group of requisite base strength. At the moment, no explanation for these anomalies can be offered, except to comment that no other current theories of drug activity are universal in their application.

Before leaving the subject of basic function, more especially that associated with the side chains, there are further relevant points. The specificity of orientation and weight of the pendant dialkylaminoalkylamino-group for optimum activity in the various drug types under discussion has already been mentioned. In the diguanide class, however, no such specificity was seen, in that, whatever variation was made in the nature of the substituents either in the benzene ring or in the diguanide chain, optimum activity was always observed with a propylamino-, and in particular an *iso*propylamino-, as the terminal group (CI). Methylamino- or dimethylamino- at this position always gave inactivity. By contrast, these small groupings provided highest activity in the seemingly closely related guanylureas (CXVIII) and guanidinobenziminazoles (CXXXVIII). Indeed the *iso*propyl homologue of the latter type was inactive.

So far the profound influence of nuclear substitution of one kind or another into the many drug types described, has not been discussed. Changes in basic properties may sometimes be concerned, but usually these would be of insufficient magnitude to account for the all-or-none effects commonly observed. For example, activation of the simple pyrimidines (IV) and (VII) by the introduction of methyl groups into position 5 hardly influenced either pK_1 or pK_2, and moreover, similar substitution in other active types had the reverse effect on biological action. Likewise, the complete inactivity of the *o*-substituted phenyldiguanides could not be explained on this basis.

Undoubtedly, the most notable changes in activity were caused by variation of substituents in the aromatic groups of the many drugs described. The position of chlorine was outstanding, and it might usefully be recalled here that this substituent occurs time and again in chemotherapeutic researches where antagonism to a growth factor is being sought. In some of the antimalarial drugs, its effect was equalled by the other halogens, in others it was almost unique. Nitro- and cyano-groups could often replace chlorine, and still give high activity, but any hypothesis which attempted to sort out potentiating substituents on the basis of inductive effect, which at first sight seemed attractive, was invalidated by the host of anomalies that could be adduced. The effect of disubstitution in a single benzene ring also produced anomalies. For instance, the 3 : 4-dichloroanilino-residue, as in (XVIII; X = Y = Cl), had little influence on antimalarial activity by comparison with 4-chloroanilino-. In the isomeric (XXIV) it completely deactivated, while in the diguanide series (CI) it gave some of the most active antimalarials known. Indeed, the effects produced in the diguanide series with respect to halogeno-substitution in general were often the opposite of those seen in the arylamino- and arylguanidino-pyrimidine prototypes.

The influence of substituents in the fused-ring systems was equally unpredictable. For instance, in the arylaminoquinazoline (LXXV) and quinoline (LXXXIII) types, the introduction of chlorine into the benzene ring of the heterocyclic nucleus (positions 6 or 7) never increased but frequently decreased therapeutic activity.

[54] Gage, *J.*, 1949, 1458. [55] *Idem, ibid.*, p. 469.

In the simpler non-aryl-substituted dialkylaminoalkylamino-quinazolines (LXXXII), -quinolines (LXXXVII), -cinnolines (XCVII), and -quinoxalines (XCV), chlorine substituents at positions 6 and 7 gave marked potentiation of activity. In the last-named class, a chlorine substituent in position 2, that is α to a heterocyclic nitrogen and therefore labile, was sufficient to induce activity in an otherwise inactive type (compare XCI, and XCIV; X = H).

Finally, the possible relevance of the mass of facts to the mode ór modes of action of the many compounds requires comment. The possible significance of a structural resemblance between some of the earlier drugs and prosthetic components of certain respiratory enzymes has already been mentioned. Apart from limited information gained by studying the effect of these drugs on bacterial growth, these notions still remain essentially speculative with respect to the substances examined, and even more so in consideration of some of the later types, in particular the diguanides, where some relation to the porphyrin enzymes has been proposed. Unfortunately, biochemical knowledge relating to the malaria parasite is extremely difficult to accumulate, and it might have been hoped therefore that some indirect evidence would have been forthcoming from a study of drug structure and antimalarial activity. The diversity of chemical types producing antimalarial action is, however, so great, that any possibility of this result's being achieved seems very remote at present. Indeed, one of the few conclusions to be drawn from this research is that a chlorophenyl residue, associated but not necessarily in conjugation with an amidine or extended amidine system, and in a structure that provides the necessary cationic functions, will more often than not lead to an active agent. What cannot be predicted on present knowledge is the intensity of action, or its relation to toxic side-effects. For the moment, then, the discovery of new antimalarial agents, and indeed of new chemotherapeutic agents of all types, still remains dependent upon the inventive and preparative ingenuity of the organic chemist.

OBITUARY NOTICES.

PERCY CORLETT AUSTIN.

1879—1950.

PERCY CORLETT AUSTIN was born at Darlington on January 4th, 1879. He was educated at the Royal Grammar School, Newcastle-on-Tyne, and awarded the Dale leaving scholarship in 1898. He became an Exhibitioner and Scholar of Emmanuel College, Cambridge, and there he read for the Natural Science Tripos, receiving an honours degree. After leaving Cambridge he carried out research for two years under Dr. Julius Schmidt at the Technischer Hochschule in Berlin, where he studied the chemistry of the nitrosates and nitrosochlorides derived from trimethylethylene. In January 1904 he was appointed research assistant to Professor A. Senier in Galway. There he worked mainly on the acridines, studying the addition of halogens and alkylmagnesium halides. Also he prepared various new and complex cyclic derivatives related to acridines. This work was carried out before the acridines attained their present importance through the discovery of the antiseptic properties of acriflavine and the special value of " Atebrin " and other acridine drugs in medicine, and, no doubt, it has been of service to numerous subsequent workers in this field. From 1907 to 1909 he held an 1851 Exhibition Research Scholarship and continued his researches at University College, London, and the Sorbonne, Paris. In 1909 he became lecturer in Organic Chemistry at University College, Reading, where he found time to work on the interaction of silver nitrate and potassium persulphate.

In 1913 Austin succeeded T. M. Lowry as lecturer in chemistry at the Westminster Training College, and, apart from an interruption of 3½ years during the war, he continued in this post until 1930. During this period he collaborated with T. M. Lowry in work on the rotatory dispersion of tartaric acid and the tartrates and was associated with him in the Bakerian lecture delivered in 1921. The work was published later in the *Philosophical Transactions* of the Royal Society. These substances possess anomalous dispersion, their rotation over part of the spectrum decreasing with decreasing wave-length and even changing in sign. Their rotation is also exceptionally sensitive to concentration and to the nature of the solvent. Lowry and Austin showed that the dispersion of these compounds could be represented very accurately by a two-term Drude equation, one term being positive and the other negative. This and other work showed that the rotatory dispersion of organic compounds can be classified as simple (requiring only one term of the Drude equation) or complex (requiring two or more terms). This proved much more satisfactory than the classification into normal and anomalous dispersion formerly employed. The positive and negative terms in the equations for tartaric acid and the tartrates were identified with the presence of two forms of these substances existing in equilibrium and differing only in the intramolecular arrangement of the hydrogen bonds. Austin's special contribution to this problem was to show that, if the relative positions of the two hydroxyl groups, or of the two carboxyl groups, or of both, were fixed by ring formation the dispersion changed from complex to simple, the rotation becoming comparatively insensitive to concentration and change of solvent at the same time. This effect could be achieved in part by the addition of excess of boric acid which partially fixed the hydroxyl groups, but the second term was not eliminated entirely. However, the formation of cyclic methylene derivatives eliminated the second term completely. The methylene diether of tartaric acid (the cyclic formal) was found to possess a high negative rotation and simple dispersion, while dimethylene tartrate (the dicyclic ether ester) possesses a high positive rotation and simple dispersion. Furthermore the dispersion of cyclic diacetyl tartaric anhydride is simple, but the ring is easily opened by hydrolysis with one molecule of water and the dispersion then becomes complex. Thus the existence of two forms possessing rotations opposite in sign and different in dispersion, which leads to complex and sometimes to anomalous dispersion, depends in some manner on the free rotation of the optically active polar groups.

During the 1914—1918 war Austin was chief chemist at H.M. Factory at Sutton Oak under the Ministry of Munitions and later at the National Filling Factory at Hereford. In September 1930 he was appointed Head of the Department of Chemistry at the Technical College, Paisley, and he held this appointment until his retirement in 1944. In addition to his research he collaborated with Professor Lowry in writing Part IV of Donnington's Class Book of Chemistry, and shortly before his retirement he edited and revised Cohen's " Theoretical Chemistry."

Austin married Muriel Carrier in 1911 and had one son. Both survive him. He possessed very great patience in developing techniques with which to achieve his objectives and his many students have cause to be grateful to him for that same quality applied to his teaching. He laid great emphasis on scientific honesty in laboratory work, and was a good literary critic taking great care that the writings of his friends and students should be clear and precise. He possessed a lively sense of humour and was the friendliest and most approachable of men. Austin died on November 3rd, 1950, and will be remembered with affection by many who owe much to his training and guidance.

E. E. WALKER.

WALTER NORMAN HAWORTH.

1883—1950.

THE death of Sir Norman Haworth on 19th March 1950 removed from our midst a most distinguished organic chemist whose strong and vigorous personality had a profound influence on scientific research and education. The family to which he belonged was well known and highly respected in the north-west of England, where it had been represented in the course of several generations by a succession of business and professional men, notably lawyers and churchmen. Walter Norman Haworth, the second son and fourth child of Thomas and Hannah Haworth, was born at Chorley, in the county of Lancaster, on 19th March 1883. His father was manager of Ryland's factory in that town and after attending the local school up to the age of fourteen, Walter Norman joined his father at Ryland's where he began to learn the trade of linoleum design and manufacture. The work required a knowledge of the use of dyestuffs and in later life Haworth was wont to attribute to this early training his first interest in chemistry and that instinct for business-like methods which remained with him throughout his life.

It soon became clear that these activities, strenuous as they were, could never satisfy the intellectual powers of the young man, and before long Haworth found means to continue his education by taking lessons from a private tutor in the neighbouring town of Preston. Despite active discouragement from his family and from friends he persisted in his studies, being fired by an ambition to pass the Entrance Examination of the University of Manchester. He did so in 1903, no mean feat in the circumstances and an indication of the brilliant intellectual powers which were ripe for development. He then entered the University of Manchester and became a pupil of W. H. Perkin, junior, who was at that time head of the Chemistry Department and at the height of his powers as leader of one of the major schools of research in the country. Haworth was described by his teachers as being a quiet, serious, and hard-working student. He made steady progress through the University curriculum and gained a First-Class Honours in Chemistry in 1906. At this stage his intention was to take a position in chemical industry after a period of research work in the Manchester laboratories. But other things were in store for him. Three fruitful years of research with Perkin were followed by the award of an 1851 Exhibition Scholarship, which he elected to hold at Göttingen in Wallach's laboratory. His experience and ability enabled him to gain the doctor's degree after only one year of study and for the second year of his Scholarship he returned to Manchester, where he continued work on the terpene group. He now had the status of Research Fellow, and in 1911, at the end of the minimum time permissible, he was awarded the D.Sc. degree of the University of Manchester.

Early in 1911 he moved to the Imperial College of Science and Technology in South Kensington as Senior Demonstrator in Chemistry under Sir Edward Thorpe. During this period, besides gaining experience in teaching and continuing vigorously with research problems, he occupied his spare time in visiting the London museums. As the result of this he acquired an astonishing knowledge of pictures, carpets, furnishings, and antique furniture.

All this, however, is to be regarded as a period of preparation during which his special powers were gradually maturing. The event which finally moulded and shaped his scientific career came in 1912 when he was appointed to a lectureship (later a readership) in chemistry in the United College of the University of St. Andrews. Here he came into contact with the new developments in carbohydrate chemistry which had been initiated by Purdie and vigorously developed by Purdie and Irvine. At long last a way appeared to be opening up for the exploration of the unknown territory of the structural chemistry of the sugars. The research laboratory in St. Andrews was an exciting and stimulating place, with Irvine as director and Purdie, although retired, still a frequent visitor and a potent influence. The importance and interest of

the problems were clear and Haworth, realizing that it was impossible to do justice simultaneously to two important fields of research, gradually relinquished work on the terpenes and concentrated more and more on the carbohydrates. During this period came the development of the method of methylation of hydroxyl groups by means of methyl sulphate and aqueous alkali. Within a short time, however, the grave events of the 1914—1918 war put an end to academic research and the St. Andrews laboratories were hurriedly organized for urgent work on the production of fine chemicals and drugs. Haworth took a notable part in this and by force of personality and skilful distribution of tasks he succeeded in obtaining regular yields of the precious materials from teams of workers, many of whom had never previously seen a test-tube. Here, as in later years, Haworth's presence in the laboratory, calm, confident, somewhat austere, outwardly imperturbable as he made a round of visits to the individual workers, unmistakably inspired the feeling that the particular problem in hand not only must, but could and would be solved.

The year 1919 brought a rapid change from war-time conditions, with a return to academic research and laboratories full to overflowing with undergraduate and postgraduate students. Structural work in the carbohydrate group was renewed with vigour, Haworth's special concern being with the disaccharides, sucrose, lactose, maltose, cellobiose, and with the trisaccharide, raffinose. As his research students quickly realized Haworth put intense effort and immense energy into the problems on which he was working, and they were expected to follow suit. In addition, however, he found time to take a full part in the pleasant social life of St. Andrews, made many friends, played tennis, and took especial pleasure in exploring the wilder and less accessible parts of the Highlands of Scotland, sometimes on foot and sometimes by motor-cycle.

It was clear to all who knew him that promotion to a chair was sure to come and it was no surprise when he was called in 1920 to Armstrong College (now King's College), Newcastle-upon-Tyne, in the University of Durham, as Professor of Organic Chemistry in succession to Samuel Smiles who had moved to King's College, London. In the following year Phillips Bedson retired and Haworth succeeded him as Head of the Chemistry Department in Armstrong College. During this period problems of accommodation for the swollen student population and for a growing research school took up much time and involved much reorganization of the laboratories. Nevertheless, the work on the oligosaccharides continued steadily and a start was made on the study of the sugar carbonates, with the result that by the end of 1922 the carbohydrate school at Newcastle was well established and was attracting an increasing number of postgraduate workers. During the early part of his stay at Armstrong College, Haworth lived in Hatfield College, Durham, making many friends in both Durham and Newcastle and doing much to promote cordial relationships between the two divisions of the University. He was largely responsible for the design and equipment of the science laboratories which were built in Durham in the early part of the decade. In 1922 he married Violet Chilton Dobbie, daughter of the late Sir James Dobbie, LL.D., F.R.S. She and their two sons, James and David, survive him. Professor and Mrs. Haworth set up house in the pleasant district of Gosforth on the edge of the Town Moor to the north of Newcastle. Here the design and cultivation of a garden began to be an absorbing interest and visitors to the house were received with a kindly, gracious, and friendly hospitality which made each visit a memorable event.

At this period much thought had to be given to the design of a new chemistry department for Armstrong College, but before this could become effective events had taken place which resulted in 1925 in Haworth's move to Birmingham as Mason Professor of Chemistry in succession to Gilbert Morgan. Haworth was thereby placed at the head of a large and active school of chemistry housed in a spacious modern building on the Edgbaston site of the University. The move involved comparatively little dislocation in the research effort. A strong nucleus of postgraduate workers moved with him to Birmingham, where the research tradition had long been established and Haworth was able to watch with satisfaction the rapid growth of the carbohydrate school in both numbers and influence. From this time onwards an increasing flow of postgraduate workers from other countries was attracted to the Birmingham laboratories to gain experience of research in sugar chemistry under his direction.

The countryside surrounding Birmingham offers a plentiful choice of pleasant residential districts, and the Haworths secured a delightful house and garden at Berkswell with a history dating from Elizabethan times. Its situation in the very heart of the country some thirteen miles east of the city provided an ideal setting for the hospitality they so generously offered alike to friends and colleagues in this country and to the numerous scientists from abroad who came to visit the research laboratories.

Not long after Haworth's arrival in Birmingham an exchange of staff was arranged with the

University of Basel as the result of which Professor F. Fichter gave a course of lectures in Birmingham and Haworth paid a long visit to Switzerland. He was received with enthusiasm and during his stay abroad he lectured to the Swiss Chemical Society at Neuchâtel (April, 1928) and the Société Chimique de France at Mulhouse (February, 1928).

Another event which had important consequences was his attendance at the Tenth Conference of the International Union of Chemistry at Liége in September 1930. Carbohydrate chemistry was one of the main subjects for discussion and Haworth had been invited to give an account of ring structures in the mono-, di-, and poly-saccharides. The conference was highly successful and was memorable for Haworth because it was here that he first met C. S. Hudson, whose work he had long admired. Two years later he was invited by the German Chemical Society to deliver a comprehensive discourse on structural features in the carbohydrate group. The lecture which he had most carefully prepared was given in German before a crowded meeting of the Society in Berlin in February 1932 and was received with enthusiastic applause.

The route from the University to Berkswell unfortunately involved an awkward motor journey through several miles of busy streets and after some years Haworth began to find the driving unduly tiring. In 1933, therefore, he decided to move to a district within easier range of Edgbaston and, assisted by his architect brother, Philip Haworth, he designed and built a house at Barnt Green on the slopes of the Lickey Hills overlooking the Worcestershire plain. In design and equipment every modern device making for comfort and ease of working was incorporated, but was combined most happily with dignity of proportion and taste in decoration and furnishing. The grounds, originally bare fields, were one of Howarth's greatest delights and interests. Laid out largely with flowering shrubs and trees set in expanses of lawn they presented in a very few years a prospect of great beauty, seen to its best advantage from the main windows of the house against the background of the distant Malvern Hills.

This knowledge of architecture and building was used to good purpose when a major building problem at the University required his attention. For some years it had been clear that the Chemistry Department at Edgbaston needed expansion and apart from this much of the elementary teaching was still being conducted in temporary laboratories which had already seen many years of service. A generous gift by A. E. Hills provided the necessary funds and in due course the new building, constructed on the most modern lines for teaching and research in organic chemistry, was opened by the President of the Royal Society, Sir Frederick Gowland Hopkins, in 1937.

For many years now Haworth had been living at too high an intensity and shortly after this a breakdown in health occurred which for some time gave cause for anxiety, but a period of rest restored his strength and when the Second World War broke out he was ready to take a strenuous and highly responsible part in work on the chemical side of the atomic energy project.

For Haworth, as for so many others, the end of the war brought little relief from the pressure of work and responsibilities. The reorganization of the laboratories for peace-time work and the rapid increase in the student population of the University provided wellnigh insuperable problems of staffing and accommodation and, in addition, the call on the services of the senior members of the University for extra-mural duties remained almost as stringent as during the war. At this period, together with many other commitments, Haworth held the Chairmanship of the Chemical Research Board of the Department of Scientific and Industrial Research, and in this task he had to face the difficult problems which arose in the course of the transition from a war-time to a peace-time programme of work at the Chemical Research Laboratory, Teddington.

He had been interested from the beginning in the publication of " Advances in Carbohydrate Chemistry " which was designed to be a medium for the provision of frequent reviews of important topics in sugar chemistry and he was the British member of the Executive Committee which was responsible for the preparation of the first volume (1945). A year later he undertook an extensive and physically exhausting tour in the United States of American and Canada, in the course of which he visited many research centres, attended the Starch Round Table at Estes Park, Colorado, and lectured to the American Chemical Society. He was received everywhere with acclamation and enjoyed especially the renewal of personal contact with C. S. Hudson.

In 1948, while still at the height of his powers as a scientist and administrator, he reached the age of sixty-five, and at the end of September he retired from his post as Mason Professor of Chemistry and Director of the Chemistry Department which he had guided with such distinction for the previous twenty-three years. The severance of the ties with Birmingham University affected him strongly, but it was a source of satisfaction to him to feel that the school of carbohydrate research in Birmingham would continue under the leadership of one of his pupils

(Professor Maurice Stacey, F.R.S.), and that active centres of carbohydrate research directed by others of his former pupils were established in many universities, including Edinburgh (Dr. E. G. V. Percival and the writer), Bangor (Professor S. Peat, F.R.S.), Bristol (Dr. J. K. N. Jones), and Minnesota (Professor F. Smith). It was characteristic of him that when his many former students and colleagues at Birmingham expressed a wish to give him some token of their esteem and good wishes on the occasion of his retirement, he chose an album containing the photographs of all those who had worked in the research laboratories at Birmingham from 1925 onwards. This was prepared and was presented to him on 1st June 1949 in the presence of a large company.

Retirement, however, brought little relaxation of effort. His advice continued to be sought and he still served on numerous boards and committees, attendance at which frequently involved him in much travelling. He was invited to represent the Royal Society at the Seventh Pacific Science Congress which was held in New Zealand in February 1949. The Congress itself extended over some three weeks, and in addition to attendance at these meetings Sir Norman and Lady Haworth visited many university centres in Australia and New Zealand. He gave a series of lectures in Sydney, Adelaide, and Melbourne, and at the invitation of the Vice-Chancellor he visited the National University at Canberra. This tour in New Zealand and Australia gave him special pleasure. He was delighted with the mental vigour and vitality he encountered and it is said that young Australian and New Zealand chemists derived great inspiration from his visits to their laboratories. In every respect this tour, whilst perhaps too strenuous for a man of his age, was a great success.

After the return from Australia less than a year remained for him. There was no hint of any slackening in his activity and his interest in carbohydrate chemistry remained undiminished. Only a few days before his death he attended, as Chairman, a Chemical Society Committee on Carbohydrate Nomenclature, when he appeared to be in excellent health and spirits and conducted the meeting with his customary zest and precision. Lady Haworth and he then spent a few days in Somerset with their younger son, and returned to their home at Barnt Green on Saturday, 18th March. There had been no warning of any trouble but shortly after their return his heart failed and the end came within a few hours, peacefully and without pain or suffering.

Haworth's reputation as a leading worker in sugar chemistry was securely established by the time he moved to Birmingham and the record of the next twenty-five years showed how much can be accomplished by single-minded devotion to the elucidation of important but extremely difficult problems by a team of workers provided with the most modern equipment. Recognition of his great work and the award of honours by British and Foreign Societies and Academies came to him in a continuous flow throughout this period. He was elected a Fellow of the Royal Society in 1928; he received the Longstaff Medal of the Chemical Society jointly with Sir James Irvine in 1933, the Davy Medal of the Royal Society in 1934, and the same Society's Royal Medal in 1942. In 1935 he was President of Section B (Chemistry) on the occasion of the meeting of the British Association for the Advancement of Science at Norwich. He was the first British organic chemist to be awarded a Nobel Prize, an honour which he shared in 1937 with Professor P. Karrer for work on carbohydrates and on vitamin-C. He was an honorary graduate of many universities, including Cambridge (Sc.D.), Queen's University, Belfast (D.Sc.), Oslo (D.Sc.), and Zürich (D.Sc.). Amongst the recognitions which he appreciated most highly was the honorary LL.D. degree which was conferred on him by his own University of Manchester in 1947. Many societies and academies accorded him honorary membership (Haarlem, Brussels, Munich, Vienna, Finland, Dublin, and the Swiss Chemical Society). He served as President of the Chemical Society during the difficult years 1944—1946, and was Vice-President of the Royal Society (1947). In the University of Birmingham he held the onerous office of Dean of the Faculty of Science for some years and was Vice-Principal (for a time Acting-Principal) for the period 1947—1948. It was a source of deep gratification to his many friends and colleagues when in 1947 he received the honour of Knighthood in recognition of his work.

Of his services to science through active membership of Boards, Committees, and Councils it is impossible to write in detail, but reference may be made to the part he played in building up the Rubber Producers' Research Association, his Chairmanship of the Chemical Panel which dealt with atomic energy research during the Second World War, his work for the Colonial Products Research Council, and his Chairmanship of the Chemical Research Board of the Department of Scientific and Industrial Research. But these activities, formidable as they were in volume and responsibility, by no means complete the story of his energetic life. Haworth never spared himself in his attention to the minutest details of the running of his department. He was meticulous in the delivery of lectures to undergraduate students and in the organization of the practical classes. He was always seeking for improved methods of teaching and was

never afraid of experimenting with the two aims of stimulating the interest of the student and providing him with a sound knowledge of the fundamentals of his subject. In lectures to student and to more mature audiences he was a master of clear and dignified expression, possessing an insight which enabled him to select the really important points and to give a sound exposition of an astonishing number of these in the course of a fifty minutes' lecture. His writings reveal a similar polished lucidity and compression, shown alike in his classical book " The Constitution of the Sugars " and in his scientific papers and reports.

Great as were his achievements and his influence in the world of science, he will live in the memory of those who knew him even more deeply for other aspects of character and personality. Foremost amongst these must be placed the kindliness, sympathetic understanding, and thoughtfulness for others, which he possessed in such marked degree. By nature he was reserved and reticent almost to a fault about himself and his own affairs and his innumerable acts of kindness were carefully hidden, becoming known only by chance to any but the recipients. All who knew him valued his wise counsel and admired the uncompromising straightforwardness of his dealings, and his loyalty to those who worked with him. He was a man of wide interests. He travelled extensively and had friends in all parts of the world. He had a deep knowledge of the classics of English literature and his retentive memory enabled him to choose with singular felicity quotations with which he illustrated his speeches and lectures. Throughout his life he was interested in painting and when he visited a foreign city he invariably spent some time in the museums and art galleries, the points which concerned him most being the design and beauty of a picture considered as a whole rather than the technical details. Despite this width of interests he had few hobbies, for the good reason that he found the main activities of his life too absorbing to leave time for them. Yet it was not the case that he was always serious and, his outward reserve completely forgotten, he was happiest and most at ease on informal occasions and in the family circle.

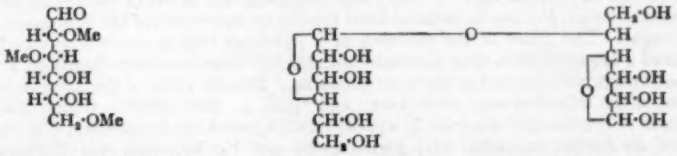
In the direction of his work in the University similar qualities were evident. His reserve tended on first acquaintance to give an impression of aloofness, but the essential friendliness very soon became evident. In the conduct of his affairs he never courted popularity and he expected those associated with him to work with the single-minded intensity of purpose which was so characteristic of his own attitude. Yet he took a keen personal interest in the welfare and activities of all the members, past and present, of his laboratory. Perhaps his most striking attribute, and one of the main reasons for his success, was a capacity for inspired leadership which created in his colleagues and research workers a passionate enthusiasm for the tasks which had been assigned to them and a determination to complete them successfully despite all difficulties. It has been given to few men to possess this characteristic so markedly and to combine with it the ability to visualize and carry through to completion in all its details a great plan of research without digressions on irrelevant side issues. His vision was directed always towards the big and important problems in carbohydrate chemistry with the ultimate object of the correlation of structure with biological function, and in following his work it is interesting to see how steadily this aim was maintained. It is significant, too, that when a second chair of chemistry was founded in the University of Birmingham it was in organic chemistry with bias towards the biological side. Yet he could not have transformed so completely the field in which he worked unless he had combined with this width of vision, a capacity for recognizing and choosing the right techniques for the solution of the day to day problems. By training he was a classical organic chemist of the older school—experience which all through his career stood him in good stead—but he was also amongst the first of the newer school in recognizing that the problems in which he was interested required a combination of the resources of modern chemistry, physics, and biology for their resolution. He saw to it that every method which could be of assistance to them was made available for the research workers in his department. The laboratory at Birmingham was one of the first in the country to have at its disposal a fully-equipped department for organic micro-analysis, which very soon served as a training centre for others who wished to use this invaluable technique. His recognition of the value of *X*-ray investigations led to the setting up of a crystallographic laboratory which under E. G. Cox (now Professor of Chemistry at Leeds) became one of the main centres of *X*-ray structural investigation in the country. Full use was made of osmotic-pressure measurements, absorption spectra, conductivity measurements, optical rotatory dispersion in the visible and ultra-violet regions and, especially during Haworth's later years, when the trend of the work became more biological, all the resources of the techniques of bacteriology and biochemistry were made available. This was accomplished largely through his wise choice in the making of appointments to the staff of the department and through it he succeeded in building up a school of research comprising many

independent workers each developing his own special interest, yet together forming a most powerful group for attacking those difficult and complicated problems which now confront investigators in the field of carbohydrate chemistry.

More than 300 communications on the chemistry of the carbohydrates were published from Haworth's laboratories during the period of some 30 years ending in 1948 and the discoveries they record were of fundamental importance in the development of the subject. It is clearly impossible to summarize these in a brief article and the most that can be attempted is to direct attention to some of the major achievements. Fortunately, Haworth has himself provided a series of general summaries which describe the various stages in the progress of his work. These include his book " The Constitution of Sugars " (1929), the lecture to the German Chemical Society (*Ber.*, 1932, **65**, *A*, 43), the Presidential Address to Section B of the British Association (1935), the Bakerian Lecture before the Royal Society (*Proc. Roy. Soc.*, 1946, *A*, **186**, 1), and his two Presidential Addresses to the Chemical Society (*J.*, 1946, 543; 1947, 582).

Haworth's earliest researches (1908—1914) were in the terpene group, his first publication being with Perkin under the title " Experiments on the Synthesis of the Terpenes." This was followed by work on derivatives of *cyclo*hexylidene-4-acetic acid and *cyclo*pentaneacetic acid. He carried out experiments with Perkin and Wallach on derivatives of menthane and sylvestrene and with Perkin on the synthesis of (+)- and (−)-sylvestrene. He had already begun to work independently and papers were published on the condensation of ketones and aldehydes with the sodium derivative of ethyl cyanoacetate, and on cantharene and other hydrocarbons related to the terpenes. This work was carried out at Manchester, Göttingen, and London (Imperial College) and was continued for a time at St. Andrews, but the last of the series was published in 1914. Haworth had by that time come under the influence of the St. Andrews school of carbohydrate chemistry and he decided to concentrate his efforts on carbohydrate problems. Early in 1915 there appeared an account of his new method of preparing the methyl ethers of sugars by the use of methyl sulphate and alkali. This had a profound effect on structural work in the sugar group and is still a standard procedure applicable alike to monosaccharides and to complex polysaccharides. Haworth undertook the study of the structure of the disaccharides, concerning which little was known with certainty except that the two monosaccharide residues were united by loss of a molecule of water. The new developments in sugar chemistry arising from the work of Purdie and Irvine offered at long last a method for solving these problems and for bringing some degree of order into the unexplored field of oligosaccharide and polysaccharide chemistry. The first step was the preparation of the fully methylated derivatives of the disaccharides, which were then subjected to hydrolysis by aqueous acid. Lactose, for example (Haworth and Leitch, *J.*, 1918, **113**, 188), gave an octamethyl derivative, which on hydrolysis yielded normal tetramethyl galactose, which had been obtained previously in the course of Irvine's pioneer work, together with 2 : 3 : 6-trimethyl glucose, the structure of which had been established by Denham. Octamethyl cellobiose (Haworth and Hirst, *J.*, 1921, **119**, 193) gave 2 : 3 : 6-trimethyl glucose and normal tetramethyl glucose, and octamethyl maltose yielded normal tetramethyl glucose and a trimethyl glucose which was finally identified as the 2 : 3 : 6-derivative, but was at first thought to be the 2 : 3 : 4-variety. Sucrose (1916 onwards) was troublesome from the start. Its octamethyl derivative gave on hydrolysis normal tetramethyl glucose and a labile form of tetramethyl fructose which was soon recognized as being related in structure to Fischer's " γ "-methylfructoside, but the nature of the ring system present in this sugar proved to be a formidable task the resolution of which required many years of patient work.

Nevertheless, considerable insight into the structures of the disaccharides was obtained in this way and it became possible to advance for them formulæ of the type shown below :



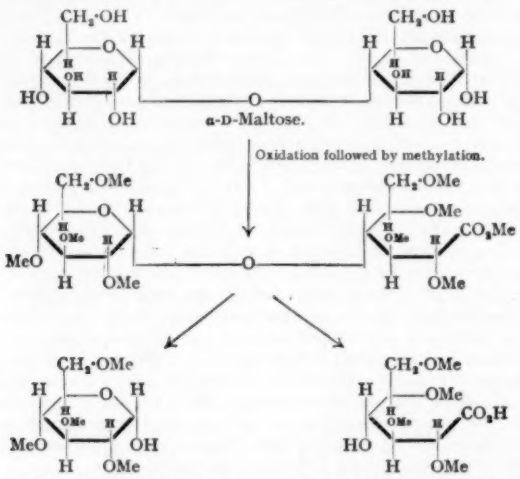
2 : 3 : 6-Trimethyl glucose. (Galactose residue.) (Glucose residue.)

Lactose.

These were, however, premature in that no sure proof had yet been given of the nature of the ring system present in normal sugars, and in 1923 when the present writer applied an oxidative

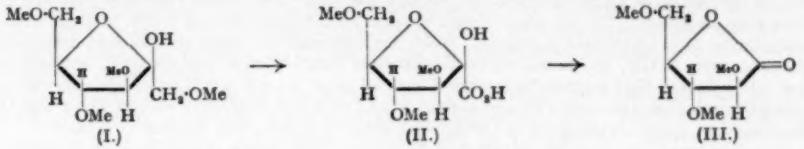
technique to the solution of this problem it was found that normal methylxyloside contained a six-membered amylene oxide ring instead of the five-membered ring structure which had hitherto been generally accepted. A full examination of the nature of the ring structure of the simple sugars became necessary and the work of Haworth and the Birmingham school on the elucidation of these problems will be considered later. It was clear also that a new approach to the disaccharide problem had become necessary when the normal sugars were shown to contain six-membered rings. It was not merely a question of change of ring, but a fundamental difficulty had arisen since the isolation of a 2 : 3 : 6-trimethyl hexose left open two possibilities, namely, a 1 : 4-oxide ring with linkage through $C_{(5)}$ or a 1 : 5-oxide ring with linkage through $C_{(4)}$. The problem was solved (with Peat, *J.*, 1926, 3094) by an ingenious development of the methylation method, which may be illustrated by its application to maltose. The sugar was first oxidized by bromine water to maltobionic acid, which on methylation gave methyl octamethyl maltobionate. On hydrolysis the latter substance was split into two fragments, 2 : 3 : 4 : 6-tetramethyl glucose and 2 : 3 : 5 : 6-tetramethyl gluconic acid. The structures of both these substances were known with certainty and the new observations, taken in conjunction with the isolation of 2 : 3 : 6-trimethyl glucose in the earlier work, established unambiguously that the disaccharide linkage was between $C_{(1)}$ of one glucose residue and $C_{(4)}$ of the other. Maltose is therefore 4-α-D-glucopyranosyl-D-glucopyranose.

By means of similar series of experiments the structures of lactose (4-β-D-galactopyranosyl-D-glucopyranose) and cellobiose (4-β-D-glucopyranosyl-D-glucopyranose) were definitely established, and by suitable modifications of the procedure structures were assigned to melibiose (6-α-D-galactopyranosyl-D-glucopyranose) and gentiobiose (6-β-D-glucopyranosyl-D-glucopyranose). The structure of the fructose residue in sucrose remained undecided for several years. The key

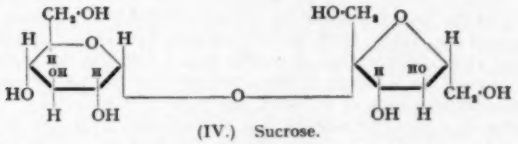


substance was the tetramethyl "γ"-fructose which appears as one of the hydrolysis products of octamethyl sucrose, but can be isolated most readily by hydrolysis of the heptamethyl derivative of the sugar. The proof of the presence of a pyranose ring in normal tetramethyl fructose eliminated a six-membered ring structure but still left open structures based on 1 : 2-, 1 : 3-, or 1 : 4-oxide rings, with the last as the most probable. Finally, proof of the furanose structure was obtained in the following way (with Avery and Hirst, *J.*, 1927, 2308). Gentle oxidation of the labile form of tetramethyl fructose (I) with nitric acid gave 3 : 4 : 6-trimethyl 2-ketogluconic acid (II), and on further oxidation with permanganic acid the keto-acid was degraded to 2 : 3 : 5-trimethyl D-arabonic acid, identified as its crystalline lactone (III). The nature of both ring systems in sucrose was then known, and, when cognisance of other evidence was taken, the structure α-D-glucopyranos-yl-β-D-fructofuranoside (IV) could be put forward for this most important of disaccharides. Once the structure of sucrose was known a combination of the results

of methylation and enzymic studies revealed the detailed structure of the trisaccharide raffinose, in which an α-galactopyranose residue is linked to $C_{(6)}$ of the glucose residue in sucrose.

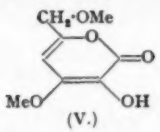


(I.) (II.) (III.)

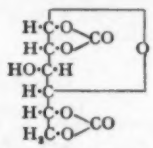


(IV.) Sucrose.

It is of interest to comment briefly on the difficulties encountered in the early work on tetramethyl fructofuranose. This reactive material gives a complex range of oxidation products, mostly liquids difficult to purify. Haworth did, however, isolate a crystalline substance with very unusual properties, to which the correct molecular formula $C_8H_{10}O_8$ was ascribed, but it is hardly surprising that this product, promising as it seemed, contributed little to the problem of sucrose structure, since it was not until eleven years later that it was recognized as being a synthetic analogue (V) of ascorbic acid which had been prepared in the course of work on the chemistry of vitamin C.



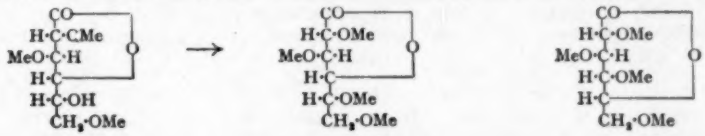
(V.)



Glucose 1 : 2-5 : 6-dicarbonate.

Simultaneously with the work on the disaccharides many other lines of investigation were being pursued in Haworth's laboratories. At Armstrong College he had commenced a study of the sugar carbonates, which can be prepared by the action of carbonyl chloride and pyridine on the sugar or sugar derivative. These proved to be of special utility in synthetic work because, being esters, they are hydrolyzed by alkalis. On the other hand they are fairly resistant to acid, in contrast with the *iso*propylidene derivatives which are not attacked by alkali but are extremely susceptible to acid hydrolysis, and as a result Haworth was able to exploit these carbonates most effectively in his work on the preparation of pure samples of the methyl glucofuranosides (see below).

A major pre-occupation of the Birmingham laboratories in the early days of Haworth's directorship was a comprehensive survey of the ring systems present in the so-called "γ" and normal forms of the methylglucosides. This work was, of course, fundamental for the whole development of sugar chemistry and without it structural determinations in the groups of the oligosaccharides and polysaccharides would have been impossible. One of the methods (*Nature*, **1925**, **116**, 430) was based on a study of the lactones of the methylated aldonic acids. For instance,



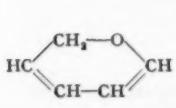
(VI.) (VII.) (VIII.)

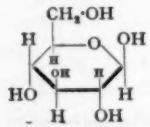
2 : 3 : 6-trimethyl glucose gives 2 : 3 : 6-trimethyl gluconic acid and the lactone (VI) of this has a rate of hydrolysis similar to those of the γ-lactones which had been used by C. S. Hudson in the formulation of his lactone rule. There is every reason therefore to suppose that it is in fact a γ- or 1 : 4-lactone. On methylation this lactone yields an equally stable tetramethyl gluconolactone

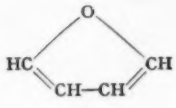
(VII), to which again the 1 : 4-structure is to be ascribed and the methyl groups must occupy positions 2, 3, 5, and 6. Now this lactone is obtained by oxidising the so-called "γ"-tetramethyl glucose derived from Fischer's labile "γ"-methylglucoside, which must therefore possess a 1 : 4-oxide ring structure. On the other hand, normal tetramethyl glucose which is obtainable by methylating 2 : 3 : 6-trimethyl glucose, yields on oxidation an entirely different tetramethyl gluconolactone (VIII), characterized by the extreme rapidity of its hydrolysis in aqueous solution. It followed that normal tetramethyl glucose must have a six-membered oxide ring and by implication this must apply also to normal α- and β-methylglucosides, results which were also established by direct application of the present writer's degradative oxidation method.

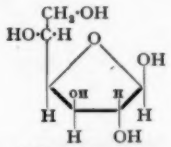
What followed can best be described in Haworth's own words, taken from his Presidential Address to Section B of the British Association in Norwich (1935). " The experimental work of the succeeding two years (*i.e.*, 1925—1927) made it possible, with the aid of colleagues and pupils, to establish the broad generalization that all normal sugars higher in the series than tetroses are constructed on the basis of the six-atom skeleton model which can be regarded now as the unit of the complex carbohydrates such as cellulose, starch, and many others. This simple model assumes the character of a sugar as soon as it is clothed with hydrogen atoms and hydroxyl groups.

" This generalization, published in 1927, had presented itself as a strong probability from the moment it was seen that the representative sugar occurring in Nature, glucose, conformed to this structural type. The experimental basis for the whole of the preliminary work was strengthened and supported by the systematic study of the sugar lactones carried out between the years 1924 and 1927. In the latter year there appeared a paper on the formulation of normal and γ-sugars as derivatives of pyran and furan, and the suggestion of a new nomenclature. The normal sugar types can all be given a standard structure recognizable under the name of a pyranose. The labile or γ-sugars, which had hitherto been but little investigated, were shown to be ascribable to the parent form of furan and therefore recognizable under a nomenclature describing them as a furanose type."

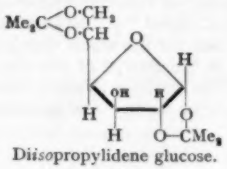

Pyran.

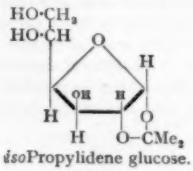

β-Glucopyranose.

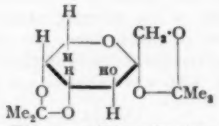

Furan.

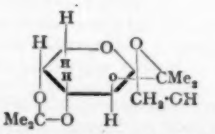

β-Glucofuranose.

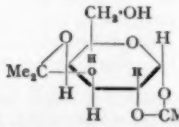
Once these fundamental structural features had been determined the way was open for structural investigations covering every aspect of carbohydrate chemistry. By use of the methylation method the structures of the *iso*propylidene derivatives of the sugars were elucidated and it appeared that with the free sugars the ring system adjusted itself during the reaction so that *cis*-hydroxyl groups on contiguous carbon atoms became available for condensation with acetone. Examples are given in the accompanying formulæ which depict di*iso*-propylidene glucose (IX), the corresponding mono-derivative (X) (furanose structures), α-di-

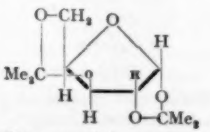

Di*iso*propylidene glucose.
(IX.)


*iso*Propylidene glucose.
(X.)


α-Di*iso*propylidene fructose.
(XI.)

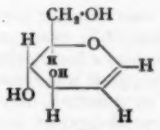

β-Di*iso*propylidene fructose.
(XII.)


Di*iso*propylidene galactose.
(XIII.)

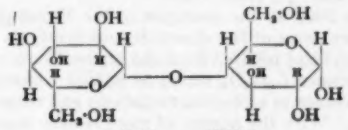

Di*iso*propylidene xylose.
(XIV.)

*iso*propylidene fructose (XI), β-di*iso*propylidene fructose (XII), and di*iso*propylidene galactose (XIII) (pyranose structures). The guiding principle is the formation of strainless ring systems and two further examples of this are 2 : 3-5 : 6-di*iso*propylidene mannose (furanose structure with free reducing group) and di*iso*propylidene xylose (XIV) where the second molecule of acetone condenses with the hydroxyl on $C_{(3)}$ and $C_{(5)}$ of the xylofuranose molecule with the forma- of a strainless six-membered ring.

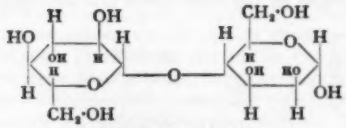
Structural work on the glucals was carried out in the Birmingham laboratories, glucal, for example, being shown to have the pyranose structure depicted in (XV). This interest in glycals had important consequences and enabled Haworth and his colleagues to resolve a difficulty which at one time appeared to threaten the very foundations of structure assignment in the sugar group. According to Hudson's iso-rotation rules the molecular rotations of the α- and the β-form of a sugar can be written as $A + B$ and $-A + B$ respectively, where A refers to the contribution of the reducing carbon atom and B to that of the rest of the molecule. The difference between the molecular rotations should therefore be $2A$, and should be independant of the sugar. For several sugars, including, for example, glucose, galactose, and xylose, this is almost exactly true and the value of A is approximately 8500. On the other hand the rotations of α- and β-mannose do not follow the rule and Hudson put forward the hypothesis that this was because the α- and the β-form of mannose possessed different ring structures. The numerical data were such that by assuming a furanose structure for normal α-methylmannoside an apparently self-consistent scheme of sugar structures could be advanced which enabled correct predictions to be made of the rotations of substances which were unknown at the time but were subsequently prepared. But according to the chemical evidence α-methylmannoside had a pyranose structure and it followed that either the methylation procedure or the iso-rotation rules must be at fault. The issue was settled by Haworth in a characteristically direct and simple way. All methods of attack were in agreement in assigning to cellobiose the structure (XVI) in which $C_{(4)}$ of the reducing glucose residue is linked to $C_{(1)}$ of the second residue.



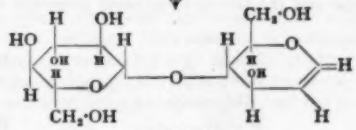
(XV.)



Cellobiose. (XVI.)

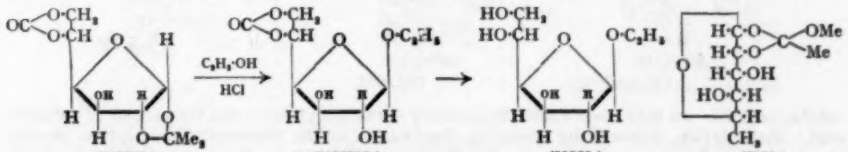


4-β-Glucosyl-α-mannose.



Cellobial.

Cellobiose cannot therefore give furanose derivatives and if the H and OH on $C_{(2)}$ of the cellobiose could be interchanged the resulting disaccharide would be a derivative of mannose which again could not react in the furanose form. This substance would therefore provide a crucial test, and means to carry it out were provided by the conversion of



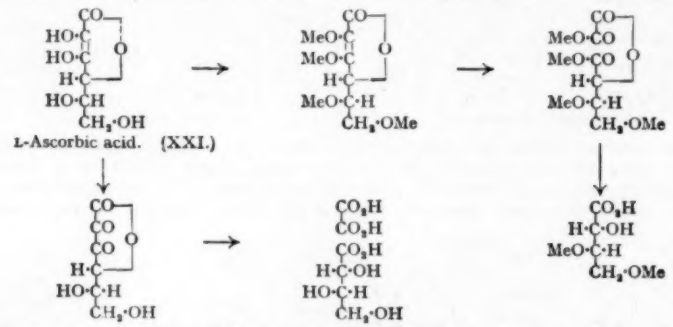
(XVII.) (XVIII.) (XIX.) (XX.)

cellobial into 4-β-glucosylmannose by the action of perbenzoic acid. The rotations of the α- and the β-forms of 4-β-glucosylmannose and of 4-β-galactosylmannose (from lactal) gave the same value for A (*ca.* 4000) as did mannose. Only one ring structure, namely the pyranose form, being possible in 4-glucosylmannose and in 4-galactosylmannose, it followed immediately

that the rotational data provided no evidence for the presence of different rings in the α- and the β-form of mannose itself and that the structural edifice built on the assumption was invalid. In a series of comprehensive papers Haworth and his collaborators proceeded to show that the rotations of sugars in which the second and the third carbon atom carry *cis*-hydroxyl groups (mannose, rhamnose) follow different numerical rules from those in which the groups are in the *trans*-position (glucose, galactose), and that the prediction of correct rotation values depended on fortuitous regularities which appear in the series of differences between the *A* values for the glucose series, the *A* values for the mannose series, and the *B* values for the pyranose and furanose varieties of the sugars (*J.*, 1930, 2615 and following papers).

Another fundamental problem which was studied at this period (1929—1932) was the preparation in a pure condition of the α- and the β-forms of methylglycofuranosides. By the usual method of preparation (methyl-alcoholic hydrogen chloride in the cold) a non-crystalline and inseparable mixture of the two forms is obtained. To obtain the pure isomers Haworth made use of the properties of the sugar carbonates. As an example the preparation of the ethylglucofuranosides will be given. 1 : 2-*iso*Propylidene glucose (X) was converted into the 5 : 6-carbonate (XVII). The latter on treatment with ethanolic hydrogen chloride gave crystalline β-ethylglucofuranoside 5 : 6-carbonate (XVIII), from which crystalline ethyl-β-glucofuranoside (XIX) was obtained by alkaline hydrolysis. By introducing a stage of acetylation, separation of the α-form of the 2 : 3-diacetyl derivative of the ethylglucofuranoside carbonate became possible and after alkaline hydrolysis ethyl-α-glucofuranoside was isolated in the pure crystalline state. The methylglucofuranosides were prepared in a similar way, and the 2 : 3-5 : 6-dicarbonate of mannose provided a starting point for the synthesis of α-methylmannofuranoside. Amongst other work in the glycoside group mention may be made of the determination of the pyranose structure of the mono-orthoacetyl derivatives of methyl rhamnoside (XX) and methyl mannoside, the triacetyl derivatives of which are found amongst the products obtained by the action of quinoline in the presence of methanol on acetobromo-sugars (with Bott and Hirst, *J.*, 1930, 1395).

In 1932 all the resources of the Birmingham laboratories were brought into play to tackle the problems of the structure and synthesis of vitamin C. Some four years previously Szent-Györgyi had isolated from the adrenal cortex and from orange juice a highly reactive substance of formulæ $C_6H_8O_6$ which he named " hexuronic acid." Although it was suspected of having importance in biological oxidations and reductions its identity as vitamin C only became known later. With the advent of more readily accessible supplies from Hungarian paprika the writer and his colleagues at Birmingham were able to begin an intensive study of its constitution which presented many most unusual features. It was shown to be stereochemically related to L-threose and the key to its general structure was provided by the observation that although the



L-Ascorbic acid. (XXI.)

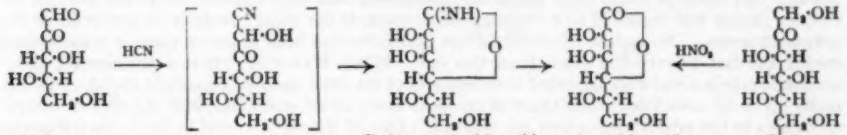
substance itself—an enol—was acidic, its primary oxidation product was the lactone of a diketo-acid. Methylation, followed by oxidative degradation of the tetramethyl derivative, showed that ascorbic acid (the new name given to the substance by Haworth when its vitamin activity was established) had the structure (XXI).

It was clear that synthesis of such a labile molecule would be a formidable task, rendered all the more difficult by the fact that the substance belonged to the relatively inaccessible L-series of sugars. But the prize, no less than the first chemical synthesis of a vitamin, was a great one, and Haworth mobilized a large team of workers, some of whom carried through pilot experi-

ments in the D-series, while the others undertook the laborious task of preparing a sufficient quantity of L-xylosone. D-Galactose was the starting material and the successive stages were di*iso*propylidene D-galactose, di*iso*propylidene D-galacturonic acid, D-galacturonic acid, L-galactonic acid, L-galactonamide, L-lyxose, L-lyxosazone, L-xylosone. In the synthesis of L-ascorbic acid, L-xylosone was made to react with hydrogen cyanide (reagents: calcium chloride and potassium cyanide), and the intermediate reaction product was hydrolyzed, giving L-ascorbic acid identical in all respects with natural vitamin C. This spectacular result was achieved simultaneously with Reichstein's synthesis by a similar process.

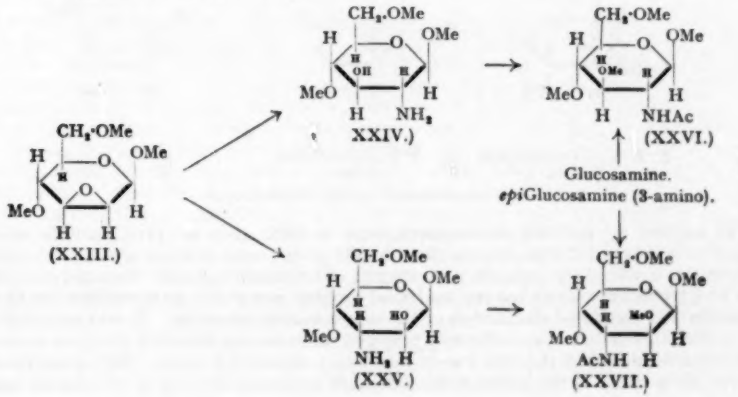
Workers in many laboratories then commenced a search for physiologically active analogues and several of these were made and studied at Birmingham. In the course of this work it was discovered that the intermediate compound in the synthesis has the imino-structure (XXII) and already contains the 1 : 4-oxide ring. Here only the briefest mention can be made of the many other problems in this field which were intensively studied in Haworth's laboratories during the next few years. They included the elucidation of the extraordinarily complicated behaviour of the monomethyl and dimethyl derivatives of ascorbic acid, the synthesis of the vitamin by direct oxidation of L-sorbose with nitric acid, and the preparation of analogues of ascorbic acid having six-membered rings. The last-mentioned series of investigations led back quite unexpectedly to the problem of the structure of "γ"-fructose when one of these analogues was found to be identical with material obtained twelve years before by the oxidation of tetramethyl γ-fructose.

Yet another example of unexpected repercussions came in the course of the next year or two when a strictly chemical proof was given of the long disputed stereochemical nature of the naturally occurring D-glucosamine (Haworth, Lake, and Peat, *J.*, **1939**, 371). This possibility arose as the result of a long series of investigations on the anhydro-derivatives of the sugars. Many types are known and both 3 : 6-anhydrides and anhydrides of the ethylene oxide type were studied in detail. The former were shown to be remarkable in undergoing ring changes



L-Xylosone. Imino-L-ascorbic acid. (XXII.) L-Ascorbic acid. L-Sorbose.

from the pyranose to the furanose type, the 3 : 6-oxygen bridge remaining intact. The ethylene oxide anhydro-sugars are equally reactive and in most instances their opening is accompanied by Walden inversion at one of the two carbon atoms. A patient and detailed study of the phenomena accompanying the formation of these anhydro-sugars on hydrolysis of an appropriate sugar 6-toluene-*p*-sulphonate and their opening by means of sodium methoxide paved the way for the solution of the glucosamine problem.



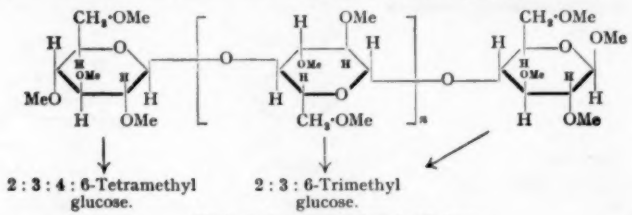
(XXIII.) (XXIV.) (XXV.) (XXVI.) (XXVII.)

Glucosamine.
*epi*Glucosamine (3-amino).

The key substance for this was 2 : 3-anhydro-4 : 6-dimethyl methyl-β-D-mannoside (XXIII) the ethylene oxide ring of which is broken by sodium methoxide with the formation of the two products, 2 : 4 : 6-trimethyl methyl-β-D-glucoside and 3 : 4 : 6-trimethyl methyl-β-D-altroside. It had been proved that similar modes of scission operate when ammonia is used in place of sodium methoxide, and with this reagent the two products (which were separated by fractional crystallization of their *N*-acetyl derivatives) must be 2-amino 4 : 6-dimethyl methyl-β-D-glucoside (XXIV) and 3-amino 4 : 6-dimethyl methyl-β-D-altroside (XXV), respectively. Of these two substances the one having the amino-group on $C_{(3)}$ was recognizable because on methylation it gave 2-amino 2 : 4 : 6-trimethyl methyl-β-D-altroside, which, being a known derivative of Fischer's *epi*glucosamine, must have the amino-group on $C_{(3)}$. The other must therefore be a derivative of glucose, and its methylation product, 2-amino 3 : 4 : 6-trimethyl methyl-β-D-glucoside, was found to be identical with the product obtained by the methylation of natural glucosamine (chitosamine). Here again proof of identity was obtained by a comparison of the crystalline *N*-acetyl derivatives (XXVI and XXVII) of the two substances. Glucosamine, therefore, is really 2-amino glucose and is not a derivative of mannose. It is of interest that E. G. Cox, working in the Birmingham laboratories, furnished an independent proof of this structure as the result of *X*-ray studies of salts of glucosamine.

These examples by no means cover the full range of investigations into the chemistry of the simple sugars carried out at Birmingham. They may suffice, however, to give some idea of the scope of the work undertaken, and the reader must be referred elsewhere for accounts of other important activities, which included a comprehensive survey, sponsored by the Colonial Products Research Council, of the chemistry of sucrose and its transformation products—mannitol, sorbitol, hydroxymethylfurfuraldehyde and many others—with the object of utilizing cane sugar as the starting material for the manufacture of organic chemicals.

The field of polysaccharides, in which Haworth made many of his most fundamental contributions, still remains for consideration. It is probably true to say that his aim had been always towards this group of biologically important substances, and that a great part of the work in the simpler groups was regarded as a stepping-stone towards the more complicated problems of the polysaccharides. No section of carbohydrate chemistry has been more completely transformed during the last twenty-five years than this one. When Haworth's studies commenced, polysaccharides in general were regarded as substances of the little understood colloid group, probably made up of an associated assemblage of comparatively small molecules, and the idea of macromolecules in the modern sense had yet to come. One of Haworth's most brilliant contributions was his immediate recognition of the significance of the *X*-ray studies of Sponsler and Dore who had interpreted their observations on cellulose in terms of long chains of glucose residues linked throughout by normal valencies. The mode of linkage they adopted involved an ether grouping, but Haworth showed that by a simple modification the idea of the cellobiose residue as a repeating unit could be incorporated, and in 1927 at the annual meeting of the Society of Chemical Industry at Edinburgh he put forward the long chain formula for cellulose which since then has been accepted as expressing the main structural features of this polysaccharide.

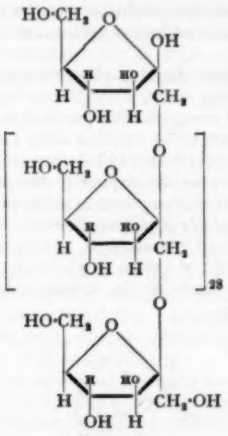


Hydrolysis of methylated cellulose.

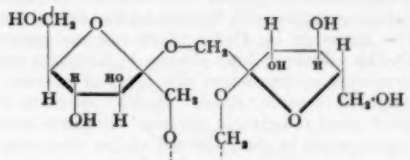
Yet another far reaching development came in 1932 when he introduced the end-group method as a means for studying the finer details of polysaccharide structure. As applied to cellulose this involved the separation of one part of tetramethyl glucose from 200 or more parts of 2 : 3 : 6-trimethyl glucose but the analytical problem was solved by a combination of solvent extraction and fractional distillation of the mixed methylglucosides. It was established that fully methylated cellulose, as ordinarily prepared, contains one terminal group for every 100—150 glucose residues and the structure is therefore a terminated chain. This achievement was followed by a study of the cellodextrins obtained by partial hydrolysis of cellulose and by a

comprehensive study of the changes in chain length which take place during the acetylation and methylation of cellulose. In its natural condition the cellulose molecule, as indicated for example by ultra-centrifuge measurements, contains more glucose residues than 150, possibly as many as 3000. The work of the Birmingham school showed that considerable shortening of the chain took place during acetylation and that the product always contained a terminal group (approximately one such group per 150 glucose residues) and similar results were obtained by direct methylation in the presence of oxygen. Much less degradation took place when methylation was conducted in nitrogen and the highly interesting result emerged that after many successive treatments of this kind a methylated derivative was obtained containing some 200 glucose residues but no end-group. Tentative explanations were advanced based on the formation of loops by the joining together of fragments of adjacent chains but the complete elucidation of this mystery has yet to be found.

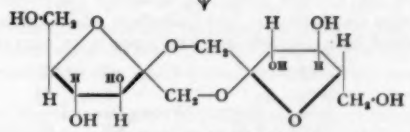
Another series of publications (1928 onwards) deals with the chemistry of inulin. This is a simpler molecule, based on 1 : 2-linked fructofuranose residues, and by application of the methylation method and end-group assay it was shown to contain approximately thirty such residues. The geometrical disposition of these provided a ready explanation of the transformation of inulin into difructose anhydrides, the structure of which was studied in detail in the Birmingham laboratories. Work was also carried out on the fructose polysaccharides present as reserve materials in meadow grass and barley leaves. These were shown to contain chains of fructofuranose units linked through $C_{(2)}$ and $C_{(6)}$.



Inulin.



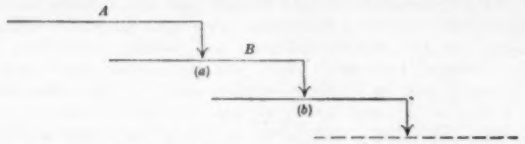
Inulin.



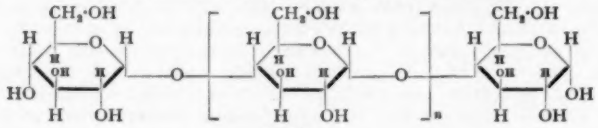
Difructose anhydride.

From 1930 onwards aspects of starch and glycogen chemistry continued to be a main feature of the work at Birmingham and in one of the earlier papers in this series a chemical proof was given (with Percival) of the presence of maltose residues in the polysaccharide. This was accomplished by a study of the controlled acetolysis of methylated starch which yielded an acetylated derivative of partially methylated maltose. This was recognized after hydrolysis, oxidation, and remethylation in the form of methyl octamethyl maltobionate. When the end-group method of investigation was applied by Plant and by Hirst to trimethyl starch the unexpected result emerged that between 4 and 5% of the glucose residues were present as terminal groups. That this was no artefact but reflected a fundamental feature of the starch molecule was proved by a careful study of the end-group assay applied to methylated starches covering a wide range of molecular weights. It was clear, therefore, that starch differed from cellulose in containing a highly branched molecular structure and the " laminated " formula was put forward (Haworth, Hirst, and Isherwood, *J.*, 1937, 578) as a diagrammatic representation of the simplest possible explanation of the observations. According to this the molecular structure consists of chains of α-1 : 4-linked glucose residues, each chain containing on the average 24 units and being joined by an ordinary glucosidic link to $C_{(6)}$ of one of the glucose units in another similar chain. This idea was applied also to glycogen in which a still higher proportion (8% for most glycogens ; 6% for occasional samples of rabbit-liver glycogen) of end-groups was observed.

When it became certain from the work of Meyer, Schoch, and other investigators that most starches consist of an intimate mixture of the two polysaccharides amylose and amylopectin, separate examination of these revealed that the branched structure applied to amylopectin,



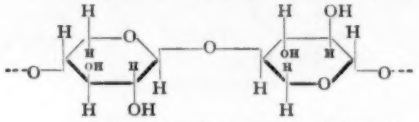
" Laminated " formula for amylopectin. *A*, *B*, etc., are unbranched chains of α-1 : 4-linked glucose residues connected at (*a*), (*b*), etc., by –G1 : 6G– linkages.



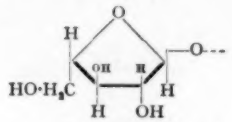
Amylose.

whereas amylose possessed a long, unbranched chain of some 100—150 α-1 : 4-linked glucose residues. Much attention was given to the problem of preparing in a pure condition samples of the two components of various starches and new methods were elaborated including the use of the crystalline complex with thymol for the separation of amylose.

The discovery by Hanes of an enzyme present in potato juice capable of synthesizing a starch-like substance from glucose 1-phosphate and of transforming starch into glucose 1-phosphate opened up important new fields of enzymic studies which were actively pursued by the Birmingham research school. Hanes's synthetic starch was shown to be amylose with a chain length of about 100 glucose residues. Inquiries (with Peat) into the relationship between amylose and amylopectin in the plant led to the discovery of another enzyme, subsequently designated "Q" enzyme, which is responsible for the formation of the branched-chain system in amylopectin. By the combined action of P and Q enzymes on glucose 1-phosphate a polysaccharide closely similar to natural amylopectin was synthesized. Other aspects of the enzymic chemistry of starch also claimed attention, including the purification and mode of action of the hydrolytic enzymes designated α- and β-amylase, and a detailed study was made of the various dextrins obtained from amylose and amylopectin by enzymic degradation.



Structural unit in xylan. (XXVIII.)

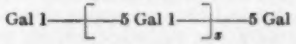


(XXIX.)

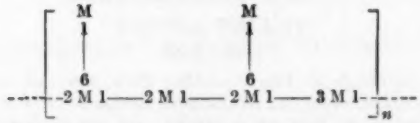
The methylation method was successfully used to determine the main structural features of many other important naturally occurring polysaccharides. An adequate summary of all this work is not practicable and only brief mention of a few items can be made here. One of the most interesting is the xylan which accompanies cellulose in esparto. This pentosan gave a dimethyl derivative which on hydrolysis yielded predominantly 2 : 3-dimethyl xylose (Haworth, Hampton, and Hirst, *J.*, 1929, 1739). The type of structure present in the xylan molecule is therefore represented by (XXVIII), but the material is of high molecular weight and a " laminated " structure of the amylopectin type was suggested for it. Some 2 : 3 : 5-trimethyl L-arabinose was identified amongst the products of hydrolysis of the methylated pentosan (Haworth, Hirst, and Oliver, *J.*, 1934, 1917) and it was shown that this arabinose residue disappeared on very mild treatment of the xylan with aqueous acid, leaving a true xylan in which one xylose residue in every 18 was present as an end-group (with Bywater, Hirst, and Peat, *J.*, 1937, 1983). It seemed probable, therefore, that in natural xylan the unit chain of some 18—20 xylose residues was terminated by arabofuranose residues (XXIX). Subsequent work, however, in other laboratories renders it more likely that the arabinose residues are actually present in a separate polysaccharide, araban, and are not linked chemically to the xylan residues.

The later part of Haworth's period as Director of the Birmingham laboratories was character-

ized by an increasing interest in the chemistry of polysaccharides of biological importance. His laboratory and Raistrick's at the London School of Hygiene and Tropical Medicine collaborated



Galactocarolose (Gal = galactofuranose residue).

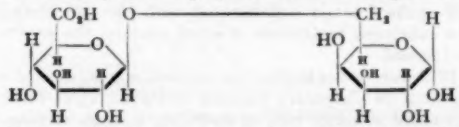


Possible representation of repeating unit in yeast mannan.

in the study of polysaccharides synthesized by micro-organisms, and joint papers were published on the structure of mannocarolose, produced from glucose by *Penicillium Charlesii* G. Smith, varianose (*P. varians* G. Smith), galactocarolose (*P. Charlesii* G. Smith), and luteose (*P. luteum*).

Many other polysaccharides of this type were also studied in the Birmingham laboratories, including the mannan from yeast and the dextrans produced by *Leuconostoc sp.*

The chemistry of the uronic acids also received attention, and amongst the earlier researches in this group the determination of the structure of the aldobiuronic acid (XXX) derived from gum arabic is noteworthy in that this was the beginning of intensive studies of the chemistry of the pectins and plant gums, which have been continued by Haworth's colleagues in the University of Birmingham and in other universities. This aldobiuronic acid was of interest also in that it had close affinities with the highly specific polysaccharides of the pneumococcus group.



(XXX.) 6-β-D-Glucuronosyl-D-galactose from gum arabic

It was appropriate that amongst the last publications bearing Sir Norman Haworth's name were two papers (with Kent and Stacey, *J.*, 1938, 1211, 1220) on the structure of two polysaccharides which are of importance in connexion with the problems of tuberculosis. In this pioneer work the methylation procedure was again utilized to obtain some insight into the constitutions of two polysaccharides, one somatic and one lipoid-bound, produced by a human strain of *M. tuberculosis*.

This survey of Haworth's achievements in chemistry cannot be concluded without reference to the important contributions to the war effort made by himself and his colleagues in Birmingham during the period 1939—1945. When the war began the laboratories were fully occupied with work on starch, bacterial polysaccharides, plant gums, and on certain aspects of the insulin problem. Late in 1939 Howarth was approached by M. L. E. Oliphant for assistance in making available quantities of metallic uranium and its numerous derivatives. He seized upon this project with his customary vigour and the various aspects of the programme were divided amongst teams of workers in the Chemistry Department. The preparation of many pounds of highly purified uranium metal was successfully completed and a wide variety of derivatives was made in the course of an intensive search for a volatile compound. Shortly afterwards (1941) Haworth became Chairman of the British Chemical Panel concerned with the atomic energy project and the scope of the work at Birmingham was much extended by the inclusion of a comprehensive series of researches into the preparation and properties of organic fluorine compounds. All this involved a close liaison with the corresponding efforts which were in progress in the United States of America and in Canada and in the course of the following two years several of Haworth's collaborators were selected to join the staff of the newly opened experimental stations at Oak Ridge (U.S.A.) and Chalk River (Canada). At the same time a considerable team remained at Birmingham where research work went on continuously into the more fundamental aspects of the chemical problems. This work imposed a heavy strain on Haworth and his responsibilities were particularly onerous in the period from 1943 onwards, when in addition to the direction of these war projects, he took a big part in organizing the Colonial Products Research Council, under whose auspices a group of research workers was established in Birmingham in 1944 for the

study of cane-sugar and starches and their transformation products. Haworth's energy and vitality at this period, when he was already over sixty years of age, appear all the more noteworthy when it is remembered that with all this he managed to combine successfully the routine duties of his Chair, the responsible and time-consuming tasks which he undertook as Dean of the Faculty of Science (1943—1946), and the many difficult problems which faced him from 1944 to 1946 as a war-time President of the Chemical Society. E. L. HIRST.

WILLIAM LOWSON.

1875—1951.

WILLIAM LOWSON died suddenly at Leeds on May 20th, 1951, at the age of 76. Born at Bridlington, he received his schooling at Bridlington Grammar School and Durham Grammar School. After leaving school he took up pharmacy and qualified as M.P.S. but, instead of continuing in this line, he attended the Yorkshire College and took the degree of B.Sc. (London) in 1900. For a short period he worked in the Government Laboratory in London, and studied for the examinations of the Institute of Chemistry, of which he became an Associate in 1901 and a Fellow in 1904. From 1901 until his death he was a Fellow of the Chemical Society. In 1903 he was appointed Demonstrator in Chemistry in the Yorkshire College, which became the University of Leeds in the following year. He took the degree of B.Sc. (Leeds) in 1905, and was promoted to Assistant Lecturer. In 1919 he was made Lecturer in Analytical Chemistry.

One of Lowson's chief interests was laboratory teaching in Inorganic and Analytical Chemistry and after a short period the organization of the courses and accessory services in all the laboratories of the Department of Inorganic Chemistry was put in his hands. As a result of his experience he published two books, " Preparations and Exercises in Inorganic Chemistry " and " Notes on Quantitative Analysis."

In the period 1925—1935 Lowson collaborated with the late Professor H. M. Dawson in an investigation of the catalysed hydrolysis of ethyl acetate, the results being published in a series of papers in the *Journal*.

During the 1914—1918 war, owing to shortage of staff, a great deal of work and responsibility in keeping the Department of Chemistry running devolved upon Lowson. Yet by working very long hours he managed to carry out, in addition, a large volume of analytical work on paints and varnishes for the War Department. When war broke out in 1939 Lowson was about to retire. As a large part of the administration and organization of the Department of Inorganic Chemistry was in his hands, his departure would have thrown a heavy burden on other members of the staff. Under the circumstances Lowson volunteered to carry on his duties for the duration of the war. This he did and enabled the Head of the Department and a team of workers to concentrate their attention on problems connected with the war.

Lowson retired at the end of the war and continued to be very active in many ways. One of his major activities was in connection with the Church of England. For over twenty years he was a Lay Reader, and week after week took services in and around Leeds. For some years he was Churchwarden of St. Chad's parish, and later was a member of the Parochial Council.

Lowson had also other and less serious enthusiasms. He was a keen and successful player of lawn tennis and played for Yorkshire in a considerable number of matches. He was the enthusiastic possessor of a motor cycle and side-car which he ran for many years, and it was with great reluctance that he exchanged it for a car when he was approaching the age of 60.

Lowson was a very conscientious man and very insistent upon accuracy in work and speech. These characteristics he tried to instil into students and others with whom he came in contact. To those who did not come up to his standards, he could make rather cutting remarks full of dry wit, but behind his words there was always a kindliness. At heart he was most kindly, and would spend any amount of time and effort to help students, members of staff, and acquaintances who were strangers to Leeds or in trouble of any kind. He was a very far-seeing man and, consequently, advice and assistance from Lowson were well worth having. He endeared himself to a very large number of students throughout his sojourn in the Chemistry Department, and when they paid visits to the Department in after years they always made a point of seeing him. He had a remarkable memory for faces and names, and a visitor whom he had not seen for twenty years would be hailed by name and reminded of the position of his bench in the laboratories.

The news of Lowson's sudden death came as a great blow to his very large circle of friends, who felt that they had sustained a great loss.

Lowson leaves a widow and a married son. J. HUME.

THE CHEMICAL SOCIETY

SCIENTIFIC MEETINGS DURING NOVEMBER, 1951

LONDON.

Thursday, November 1st, 1951, at 7.30 p.m.

The following papers will be read and discussed:

"The Relation between Configuration and Conjugation in Diphenyl Derivatives. Part I. The Optical Resolution and Ultra-violet Absorption Spectra of Some 2:2′-Bridged Compounds." By G. H. Beaven, D. Muriel Hall, Mary S. Lesslie, and E. E. Turner.

"Polyene Acids. Part II. The Stereochemistry of the β-Methylmuconic Acids." By J. A. Elvidge, R. P. Linstead, and P. Sims.

"Polyene Acids. Part III. A Re-investigation of Karrer's β-Methylmuconic Acid." By J. A. Elvidge, R. P. Linstead, and P. Sims.

"Structural Investigations of Co-enzyme A." By J. Baddiley and E. M. Thain.

Thursday, November 15th, 1951, at 7.30 p.m.

The following papers will be read and discussed:

"The Photochemical Interaction of Anthracene and Alkyl Chlorides." By E. J. Bowen.

"The Photochemical Decomposition of Keten in Light of Very High Intensity." By K. Knox, R. G. W. Norrish, and G. Porter.

"Fluorescence from Formic Acid and Methylene Iodide." By P. J. Dyne, D. W. G. Style, and J. C. Ward.

ABERDEEN.

Thursday, November 15th, 1951, at 7.30 p.m.

Lecture, **Mould Metabolic Products,** by Professor A. Robertson, M.A., Ph.D., F.R.S.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemistry Department, Marischal College, Aberdeen.

BRISTOL.

Thursday, November 1st, 1951, at 7 p.m.

Lecture, **Modern Applications of Analysis,** by Mr. R. Belcher, B.Sc., F.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemistry Department, The University, Bristol.

Thursday, November 22nd, 1951, at 7 p.m.

Lecture, **Developments in Antibiotics,** by Dr. B. K. Kelly.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemistry Department, The University, Bristol.

Thursday, November 29th, 1951, at 7 p.m.

Lecture, **Recent Advances in Coal Science,** by Dr. R. Gordon.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held at the Technical College, Gloucester.

EXETER.

Friday, November 23rd, 1951, at 5 p.m.

Lecture, **Recent Work on Inorganic Oxides,** by Dr. J. S. Anderson, M.Sc., A.R.C.S.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Washington Singer Laboratories, Prince of Wales Road, Exeter.

GLASGOW.

Friday, November 16th, 1951, at 7.15 p.m.

Lecture, **Aluminium Halide as a Reagent in Organic Chemistry,** by Dr. G. Baddeley, M.Sc.

To be given at the Royal Technical College, Glasgow.

HULL.

Thursday, November 22nd, 1951, at 6 p.m.

Lecture, **The Structural Chemistry of Colchicine and Some of its Biological Properties,** by Professor J. W. Cook, D.Sc., F.R.S.

To be given in the Science Lecture Theatre, University College, Hull.

IRISH REPUBLIC.

Friday, November 9th, 1951, at 8 p.m.

Lecture, **Reactions of Hydrocarbon Radicals,** by Professor C. E. H. Bawn.

Joint meeting with the Werner Society to be held in the Chemistry Department, Trinity College, Dublin.

LEEDS.

Monday, November 5th, 1951, at 6.30 p.m.

Lecture, **The Ubiquitous Chemist,** by Mr. H. W. Cremer, C.B.E., M.Sc., F.R.I.C.

To be given in the Department of Chemistry, The University, Leeds. Royal Institute of Chemistry Lecture to which all Fellows are invited.

Thursday, November 22nd, 1951, at 6.30 p.m.

Official Meeting. Tilden Lecture, **Some Recent Developments in the Chemistry of Free Radical Reactions in Solution,** by Professor D. H. Hey, D.Sc., F.R.I.C.

To be held in the Department of Chemistry, The University, Leeds.

MANCHESTER.

Thursday, November 1st, 1951, at 6.30 p.m.

Meeting for the reading of original papers.

To be held in the Robert Robinson Lecture Theatre, The University, Manchester.

Wednesday, November 14th, 1951, at 6.30 p.m.

Lecture, **Anatomy of the Chemist**, by Dr. T. S. Stevens, A.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held at the College of Technology, Manchester.

(*Note.*—This meeting was originally arranged for November 15th.)

NEWCASTLE AND DURHAM.

Friday, November 9th, 1951.

Meeting for the reading of original papers.

To be held in the Chemistry Building, King's College, Newcastle-on-Tyne.

Wednesday, November 21st, 1951, at 7.45 p.m.

Lecture, **The Structural Chemistry of Colchicine,** by Professor J. W. Cook, D.Sc., F.R.S.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemistry Department, Science Building, South Road, Durham.

Friday, November 23rd, 1951, at 5.30 p.m.

Bedson Club Lecture, **The Transfer of Hydrogen between Organic Compounds,** by Professor R. P. Linstead, C.B.E., D.Sc., F.R.S.

To be given in the Chemistry Building, King's College, Newcastle-on-Tyne. All Fellows are invited.

NORTH WALES.

Thursday, November 8th, 1951, at 5.45 p.m.

Lecture, **New Methods of Following the Course of Chemical Reactions,** by Professor H. W. Melville, D.Sc., F.R.S.

Joint meeting with the U.C.N.W. Chemical Society to be held in the Department of Chemistry, University College of North Wales, Bangor.

NORTHERN IRELAND.

Tuesday, November 13th, 1951, at 7.15 p.m.

Lecture, **The Organic Chemist's Approach to the Chemotherapy of Tuberculosis,** by Dr. V. C. Barry, M.Sc., F.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Lecture Theatre, Department of Chemistry, Queen's University, Belfast.

NOTTINGHAM.

Tuesday, November 6th, 1951, at 5 p.m.

Lecture, **Molecular Compounds,** by Mr. H. M. Powell, M.A.

Joint meeting with Leicester University College Chemical Society to be held in the Chemistry Lecture Theatre, University College, Leicester.

Thursday, November 8th, 1951, at 4.45 p.m.

Lecture, **Some Problems concerning the Synthesis of Carbohydrates by Plants,** by Professor E. L. Hirst, M.A., Ph.D., F.R.S.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Nottingham.

Thursday, November 22nd, 1951, at 4.45 p.m.

Lecture, **Reactions of Hydrocarbon Radicals,** by Professor C. E. H. Bawn, Ph.D.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Nottingham.

OXFORD.

Monday, November 5th, 1951, at 8.15 p.m.

Alembic Club Lecture, **Steric Retardation and Steric Acceleration,** by Professor E. D. Hughes, D.Sc., F.R.S.

To be given in the Physical Chemistry Laboratory, South Parks Road, Oxford. All Fellows are invited.

Monday, November 26th, 1951, at 8.15 p.m.

Alembic Club Lecture, **Chemistry and Atomic Power,** by Dr. R. Spence, F.R.I.C.

To be given in the Physical Chemistry Laboratory, South Parks Road, Oxford. All Fellows are invited.

ST. ANDREWS AND DUNDEE.

Friday, November 2nd, 1951, at 5.15 p.m.

Lecture by Professor F. G. Tryhorn, D.Sc.

Joint meeting with St. Andrews University Chemical Society to be held in the Chemistry Department, United College, St. Andrews.

Wednesday, November 14th, 1951, at 5.15 p.m.

Lecture, **William Higgins (1763—1825): His Life and Work,** by Professor T. S. Wheeler, D.Sc., F.R.I.C.

Joint meeting with St. Andrews University Chemical Society to be held in the Chemistry Department, United College, St. Andrews.

Friday, November 16th, 1951, at 5.15 p.m.

Lecture, **The Transfer of Hydrogen between Organic Compounds,** by Professor R. P. Linstead, C.B.E., D.Sc., F.R.S.

To be given in the Chemistry Department, United College, St. Andrews.

SHEFFIELD.

Thursday, November 8th, 1951, at 5.30 p.m.

Lecture, **The Synthesis of Sugars,** by Dr. J. K. N. Jones, M.Sc., A.R.I.C.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Sheffield.

Thursday, November 29th, 1951, at 5.30 p.m.

Lecture, **Natural Complex Pyrylium Bases,** by Professor A. Robertson, M.A., Ph.D., F.R.S.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University Sheffield.

SOUTHAMPTON.

Friday, November 2nd, 1951, at 5 p.m.

Lecture, **The Chemistry of Co-enzyme A,** by Dr. J. Baddiley.

Joint meeting with Southampton University College Chemical Society to be held in the Physics Department, University College, Southampton.

Friday, November 16th, 1951, at 5 p.m.

Lecture, **The Modern Theory of Aromatic Systems,** by Dr. H. C. Longuet-Higgins, M.A.

Joint meeting with Southampton University College Chemical Society to be held in the Physics Department, University College, Southampton.

SOUTH WALES.

Friday, November 9th, 1951, at 5.30 p.m.

Official Meeting for the reading of original papers.

To be held in the Chemistry Department, University College, Swansea.

PROCEEDINGS

OF THE

CHEMICAL SOCIETY

OFFICIAL ANNOUNCEMENTS

RESEARCH FUND.

A meeting of the Research Fund Committee will be held in November next. All persons who have received grants, and whose accounts have not been declared closed by the Council, are informed that reports must be received by the Society not later than November 1st, 1951.

Applications for grants, to be made on forms obtainable from the General Secretary, must be received on or before November 1st, 1951. Applications from Fellows will receive prior consideration.

Attention is drawn to the fact that the income arising from the donation of the Worshipful Company of Goldsmiths is principally devoted to the encouragement of research in inorganic and metallurgical chemistry, and that the income from the Perkin Memorial Fund is to be applied to investigations relating to problems connected with the coal-tar and allied industries.

CORDAY-MORGAN MEDAL AND PRIZE.

The Corday–Morgan Medal and Prize, consisting of a Silver Medal and a monetary Prize of 150 Guineas, is awarded annually to the chemist of either sex and of British Nationality, who, in the judgment of the Council of the Chemical Society, shall have published during the year in question, the most meritorious contribution to experimental chemistry and who shall not, at the date of publication, have attained the age of thirty-six years. The Council has power to suspend the award in any year in which no suitable candidate presents himself or is brought to the notice of the Council.

Copies of the rules governing the Award may be obtained from the General Secretary of the Society. Applications or recommendations in respect of the Award for the year 1950 must be received not later than December 31st, 1951, and applications for the Award for 1951 are due before the end of 1952.

LIST OF APPLICATIONS FOR FELLOWSHIP

(Fellows wishing to lodge objection to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the Journal *for October,* 1951. *Such objections will be treated as confidential. The forms of application are available in the Library.)*

Bellin, Stuart Arnold, M.S. (Wisconsin). American. Department of Biochemistry, University of Wisconsin, Madison 6, Wisconsin, U.S.A. Graduate Student and Research Assistant. *Signed by:* William S. Johnson, S. M. McElvain, Gordon M. Tener.

***Bramley, Jack Gordon,** B.Sc. (Leeds), A.R.I.C. British. 30, Westminster Road, Morecambe, Lancs. National Service. *Signed by:* E. G. Cox, J. W. Baker, P. A. Briscoe.

***Branch, Ronald Frederick,** B.Sc. (Lond.), A.R.I.C. British. 49, Bromhall Road, Becontree, Essex. Student. *Signed by:* J. Ratcliffe, D. R. J. Boyd, E. de Barry Barnett.

Burton, John James, B.Sc. (Lond.), A.R.I.C. British. 83, Porter Road, Derby. Teacher. *Signed by:* J. C. Roberts, D. O. Jordan, C. C. Addison.

***Calderbank, Kingsley Edward,** M.Sc. (Sydney). British. Fuels Division of Industrial Chemistry, C.S.I.R.O., Fisherman's Bend, Victoria, Australia. Research Officer. *Signed by:* R. J. W. Le Fèvre, T. Iredale, H. C. Freeman.

***Carter, Philip Hugh.** British. Briar Dene, Worcester Road, West Hagley, Stourbridge, Worcs. *Signed by:* G. D. Parkes, F. M. Brewer, L. A. K. Staveley.

Chargaff, Erwin, Dr.phil. (Vienna). American. Cell Chemistry Laboratory, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York 32, N.Y., U.S.A. Associate Professor of Biochemistry. *Signed by:* A. R. Todd, A. J. Birch, S. F. MacDonald.

Collett, Esmond Frank, B.Sc. (Dunelm and Nottingham). British. 183, Fambridge Road, Malden, Essex. Research Chemist, Marconi Research Laboratory, Gt. Baddow, Essex. *Signed by:* B. D. Shaw, F. C. Cooper, C. C. Addison.

Eastham, Arthur Middleton, M.A. (British Columbia), Ph.D. McGill). Canadian. National Research Council of Canada, Division of Applied Chemistry, Ottawa, Canada. Research Chemist. *Signed by:* L. C. Leitch, Bryce Douglas, B. de B. Darwent.

***Fleetwood, John George,** B.Sc. (Birm.). British. Lyndhurst, Bernard Street, Walsall, Staffs. Research Student, Birmingham University. *Signed by:* Arthur E. James, E. J. Bourne, W. Wilson.

Hurford, James Hugh Fraser, M.P.S. British. 346, York Road, Wandsworth, S.W.18. Company Director. *Signed by:* Arthur Mortimer, Reginald Goode, J. Ross-Mansell.

Isherwood, Raymond Charles, B.Sc. (Lond.). British. 12, The Front, Potters End, Berkhamsted, Herts. Industrial Chemist, Brandhurst Co., Ltd., E.C.4. *Signed by:* C. S. Salmon, R. Schaffer, D. H. Hey.

Jeffreys, John Alexander David, B.A. (Oxon.). British. Exeter College, Oxford. Research Student. *Signed by:* Harry Irving, J. A. Barltrop, R. M. Acheson.

***Lockhart, Ian Moyle.** British. 67, Beddington Gardens, Carshalton, Surrey. Student, Lincoln College, Oxford. *Signed by:* Harry Irving, L. J. Goldsworthy, R. E. Richards.

***McCollum, John David,** B.S. (Illinois), A.M. (Harvard). American. 122, Mt. Aubern Street, Apt. 7b, Cambridge 38, Massachusetts, U.S.A. Student at Harvard University. *Signed by:* Frederick D. Greene, Jerrold Meinwald, Richard K. Hill, John T. Rundquist.

***McCoy, Layton Leslie,** B.S. and Ph.D. (Washington). American. Department of Chemistry, Columbia University, New York 27, New York. Instructor of Chemistry. *Signed by:* Kenneth B. Wiberg, H. J. Dauben, A. G. Anderson.

***Newman, Frank Christopher.** British. 36, Bulstrode Avenue, Hounslow, Middlesex. Research Student at King's College, London. *Signed by:* S. Harper, J. Sandiford, R. E. Stedman.

Robertson, Clement Moxham. British. 37, Trewsbury Road, Sydenham, S.E.26. Assistant Experimental Officer in Chemical Inspectorate, Ministry of Supply. *Signed by:* E. W. S. Press, A. S. Nickelson, J. D. Strickland.

Thomas, Norman William, B.S. (Wayne). American. 606, West Ohio Street, Urbana, Illinois, U.S.A. Student. *Signed by:* Bruce Bright, Edward C. Taylor, John K. Williams.

***Twigg, George Daniel,** B.Sc. (Lond.). British. Talbot Cottage, Alderley Edge, Cheshire. Research Chemist, Bengers Ltd. *Signed by:* Maurice E. H. Fitzgerald, Norman R. Campbell, Norman Evers.

Withey, Donald Sidney, B.Sc. (Lond.), A.R.I.C. British. 35, Florida Road, Thornton Heath, Surrey. Assistant Chemist at the British Oxygen Co., Ltd. *Signed by:* S. A. Miller, G. A. Weeks, N. E. Williams.

UNDER SPECIAL PROVISION APPERTAINING TO CANDIDATES RESIDENT ABROAD.

Colton, Frank, M.S. (Northwestern), Ph.D. (Chicago). Polish. 6455, N. Washtenaw, Chicago 45, Ill. U.S.A. Research Chemist, G. D. Searle & Co. *Signed by:* R. M. Dodson.

Faseeh, Saiyid Ahmad, M.A. (Allahabad), M.Sc. and Ph.D. (Lucknow), Pakistani. Panjab University Institute of Chemistry, Lahore, Pakistan. Teaching and Research. *Signed by:* M. I. D. Chughtai.

Horwitz, Lester, B.A. (Brooklyn College), Ph.D. (New York). American. Schenley Laboratories, Lawrenceburg, Indiana, U.S.A. Research Chemist. *Signed by:* Joseph Brenner.

Schindler, Othmar, Dr.phil. (Basle). Swiss. Hermann Suterstr. 4, Basle. Research Assistant. *Signed by:* T. Reichstein.

Trujillo, Ramon. Spanish. Facultad de Ciencias, La Laguna, Canary Islands. Professor of Chemistry. *Signed by:* M. Lora.

Wasserman, Harry H., M.A. and Ph.D. (Harvard). American. Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut, U.S.A. Assistant Professor of Chemistry. *Signed by:* Harold H. Zeiss.

* Reduced annual subscription.

PAPERS RECEIVED

(List of papers received between August 22nd and September 17th, 1951.)

"Antimalarial activity in 2 : 4-diamino-5-arylpyrimidines. Some reactions of α-formylphenylacetonitrile." By B. H. CHASE, (MISS) J. P. THURSTON, and J. WALKER.

"2- and 5-Fluoronicotinic acids." By R. D. BEATY and W. K. R. MUSGRAVE.

"The orientation of some substitution products of 7 : 8-benzoquinoline." By J. A. BARLTROP and K. E. MACPHEE.

"The infra-red spectra of some organophosphorus esters." By L. J. BELLAMY and L. BEECHER.

"Constituents of the leaves of *Psidium guaijava, L.* Part I. Psidiolic acid." By G. SOLIMAN and M. K. FARID.

"The electrolytic reductive coupling of *p*-dimethylaminoacetophenone and *p*-methoxyacetophenone." By H. A. LEVINE and M. J. ALLEN.

"The mechanism of the alkaline cleavage of some γ-pyrones." By H. R. V. ARNSTEIN and R. BENTLEY.

"1 : 2-Dihydro-2-thianaphthalene derivatives. Part II. Conversion of 1 : 2-dihydro-1-keto-2-thianaphthalenes into indanones." By D. J. DIJKSMAN and G. T. NEWBOLD.

"The interaction of α-amino-nitriles with aldehydes and ketones." By A. C. DAVIS and A. L. LEVY.

"The chemistry of subterranean clover. Part I. Isolation of formononetin and genistein." By R. B. BRADBURY and D. E. WHITE.

"The kinetics of the dissolution of zinc in aqueous iodine solutions. Part III." By A. C. RIDDIFORD and L. L. BIRCUMSHAW.

"The kinetics of the dissolution of zinc in aqueous iodine solutions. Part IV." By A. C. RIDDIFORD and L. L. BIRCUMSHAW.

"Studies of the structure of emetine. Part V. The structure of the rubremetinium salts." By H. T. OPENSHAW and H. C. S. WOOD.

"Fluorene-2-aldehyde." By S. J. ANGYAL, G. B. BARLIN, and P. C. WAILES.

"The nature of the co-ordinate link. Part V. The equilibrium between *cis*- and *trans*-bis(triethylphosphine)dichloroplatinum." By J. CHATT and R. C. WILKINS.

"The oxidation of monoethenoid fatty acids and esters. Union of gaseous oxygen with ethyl, *n*-propyl, and *n*-butyl oleate." By A. J. FEUELL and J. H. SKELLON.

"Condensation of *o*-acetoxybenzaldehyde with malonic acid and ethyl malonate." By P. M. BHARGAVA and S. HUSAIN ZAHEER.

"The synthesis of certain trifluoromethyldiphenyl derivatives." By M. R. PETTIT and J. C. TATLOW.

"The heat of nitrolysis of hexamine in nitric acid." By W. J. DUNNING, B. MILLARD, and C. W. NUTT.

"The structure of sterculic acid." By J. R. NUNN.

"Some 7-substituted derivatives of the 5α-pregnane series." By W. KLYNE.

"Pernitrous acid. The reaction between hydrogen peroxide and nitrous acid, and the properties of an intermediate product." By E. HALFPENNY and P. L. ROBINSON.

"The nitration and hydroxylation of aromatic compounds by pernitrous acid." By E. HALFPENNY and P. L. ROBINSON.

"The nitration and hydroxylation of chlorobenzene by pernitrous acid." By E. HALFPENNY, J. J. HILLARY, and P. L. ROBINSON.

"Deoxy-sugars. Part XXIII. An extension of the investigation of the Dische reaction." By R. ALLERTON, W. G. OVEREND, and M. STACEY.

"Mechanism of the reaction of terminal vicinal ditoluene-*p*-sulphonyl hexitol derivatives with sodium iodide in acetone." By A. B. FOSTER and W. G. OVEREND.

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